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THE TREATMENT OF AMOEBIASIS<sup>1</sup>

## WITH SPECIAL REFERENCE TO CHRONIC AMOEBC DYSENTERY

By W H HARGREAVES

*ENTAMOEBIA HISTOLYTICA* is the most important of the intestinal protozoa from the medical point of view. Its distribution is world-wide, and in Britain a considerable proportion of the population, probably between 7 and 10 per cent, are healthy carriers (Dobell, 1921). Amoebiasis is essentially a disease of the tropics and sub-tropics, but occasionally it may occur in this country in persons who have not been abroad, and it must always be kept in mind in cases of ulcerative colitis (Lockhart-Mummery, 1944). The extensive water-borne outbreaks of amoebic dysentery which occurred in Chicago in 1933 and 1934 showed that the incidence of the disease might reach serious proportions even in a temperate zone (Bundesen, 1934, Hardy and Spector, 1935). Unfortunately, there is a widespread belief amongst practitioners in this country that hypodermic injections of emetine will cure amoebic dysentery, this fallacy was disproved during the war of 1914-18, but it is still so general that to the average practitioner the mere suggestion of amoebiasis serves as an indication for uncontrolled emetine injections (Manson-Bahr, 1944). This is to be deplored, because if the disease is promptly diagnosed and properly treated it usually responds to specific treatment, but if it becomes chronic it leads to much suffering and may prove fatal. Injections of emetine hydrochloride are certainly specific for amoebic infection of the liver, but cure only a small number of bowel infections, according to Craig (1935) not more than 15 per cent. During the war of 1914-18 physicians in this country were confronted by large numbers of men who had developed amoebiasis overseas and came home as invalids, and pioneer work was done then in the diagnosis and treatment of the infection. In the years of peace which followed, this work was largely forgotten and general interest in the subject waned, only to be revived during the war of 1939-45, when the same problem recurred and to a greater extent. The history of many of the invalids returning to this country last year dated from the fall of Burma in 1942, when conditions were difficult, and in many instances men with dysentery on reaching India had to be treated as out-patients at hospitals which were overflowing. Drugs were scarce and malnutrition and malaria were rife amongst the men who escaped back into India, so it is not surprising that these chronic cases occurred (Hargreaves, 1945). In 1944, Leishman

<sup>1</sup> Received August 30, 1945



and Kelsall, in a review of their previous year's medical work in a hospital in India, stated that one soldier in every four admitted to the hospital with diarrhoea was suffering from amoebic dysentery. At the present time, some millions of British and American troops are serving in the tropics, so that a 'considerable virgin soil is accessible for *E. histolytica*, and according to Marriott (1945), in the South East Asia Command the problem of diarrhoea and dysentery is second only to that of malaria, and amoebae have been isolated in 20 per cent of such cases. It seems inevitable, therefore, that many more sufferers from amoebiasis will continue to present themselves in hospital and private practice throughout this country, calling for accurate diagnosis and efficient treatment. Unfortunately, however, the number of pathologists and technicians competent to examine stools for protozoal infections is remarkably small (Adams, 1944), and the treatment of chronic amoebiasis is more than a matter of simple routine, in fact it presents one of the major problems of tropical medicine (Napier, 1943).

### *Specific Drugs*

The number of methods of treatment which have been advocated for amoebiasis and for which success has been claimed is almost bewildering. Dysenteric symptoms are sometimes cured by rest in bed and nursing alone, passing off spontaneously without any other treatment, but in all such cases the patient becomes a convalescent carrier of the parasite, remaining infected and liable to relapse at any time (Dobell and O'Connor, 1921). Specific curative action, therefore, cannot be claimed for any drug until, in addition to the clinical recovery of the patient, there is conclusive evidence from adequate microscopic examinations of the stools after its administration that he is no longer infected with *E. histolytica*, and of course there must be no possibility that the original diagnosis was incorrect, and no question of the competence of the protozoologist who made the negative examinations. The approximate value of 'negative examinations' of the stools was shown by Dobell (1917), and Dobell and O'Connor (1921) considered it desirable to keep all treated cases under protozoological observation for at least a month after treatment. In the Services it is insisted as a rule that before a patient leaves hospital he must have had adequate tests of cure, and if he reports sick again at his unit he is usually sent back to hospital. This is a different state of affairs from civil life, where the patient's time may be precious and he may hesitate to report relapses for fear of being laid up again for more treatment. This may possibly be one of the reasons why some of the forms of treatment which in peace-time were considered to be successful have been found unsatisfactory during recent years.

*Emetine* must be given first place in any review of specific remedies, not only for historical reasons, but because in fact it has a more specific action on *E. histolytica* than any other available drug (Adams, 1944). *Emetine* is one of the alkaloids obtained from *ipecacuanha*, the root of the Rubiaceae plant

*Cephaelis ipecacuanha* or Brazil Root Originally a native remedy in South America, ipecacuanha was introduced into Europe in the seventeenth century, being sold to the French Government as a secret remedy and used by Helvetius, who treated Louis XIV with it. After this, its use for dysentery became widespread, and it was employed empirically until Vedder (1911, 1912), as a result of his experiments on the action of emetine on free-living amoebae, suggested its use in amoebic infections. Then followed Rogers's (1912) classical work, which showed that soluble salts of emetine, given hypodermically, had a specific action in amoebic dysentery and hepatitis. His results were dramatic, and subcutaneous injections of emetine hydrochloride still remain the specific treatment for amoebiasis of the liver. The optimum dose for an adult is 8 to 12 grains, given daily in injections of one grain, and acute amoebic hepatitis responds quickly to this treatment, the symptoms usually subsiding in two or three days. Small intrahepatic abscesses yield rapidly to emetine therapy, and the necrotic tissue becomes absorbed without necessitating free drainage (Manson-Bahr, 1943). When the amount of pus is too large to be absorbed, aspiration combined with emetine treatment is effective, and open drainage is not usually necessary unless secondary infection has taken place. Pulmonary and cutaneous amoebiasis also react readily to injections of emetine. Deep subcutaneous or intramuscular injections are better tolerated and less painful than hypodermic injections of emetine, which are liable to cause eczematous patches (Manson-Bahr, 1943). Emetine may be given intravenously, but this route has no advantage over the others, and toxic effects are more likely to result. The fact that amoebic hepatitis is cured dramatically by emetine injections is so well known that this is probably responsible for the prevailing belief that this form of treatment cures amoebic dysentery. At the beginning of the war of 1914-18, emetine injections were in vogue for this disease, but even then it was realized that although the treatment controlled the dysenteric symptoms it did not always cure the infection, and in 1917 Dobell found that full courses of daily injections of emetine hydrochloride, 10 to 12 grains or more, were successful only in about one-third of these cases.

*Emetine Bismuth Iodide (EBI)* Du Mez (1915) first suggested the use of EBI in amoebic dysentery, but an analogous compound, emetine mercuric iodide, had been prepared by Warden in 1891, and Walsh (1891) reported favourably upon its clinical effects in cases of dysentery. This, of course, was before Schaudinn (1902) identified *E. histolytica* and recognized its pathogenicity. Dale (1916) suggested that in the cases which were not cured by emetine given hypodermically, the drug failed to reach all the amoebae in the bowel wall, and he found that EBI given by mouth cleared cases which had resisted all attempts by injection. Low and Dobell (1916) were convinced that EBI by mouth was more effective than emetine injections in curing chronic carriers, and held that it should thenceforward be generally employed in such cases, at all events until a more effective treatment was forthcoming. In 1918, a team of workers headed by Dobell published the

results of an investigation undertaken for the Medical Research Committee, consisting of a study of 1,300 convalescent cases of dysentery. On bacteriological examination of the stools of these 1,300 patients, no *B dysenteriae*, *B typhosus*, or *B paratyphosus*, were isolated, but 156 were found to be infected with *E histolytica*. These cases were treated with EBI, and the conclusion was that 95 per cent of all carriers of *E histolytica* could be cured by the administration of this drug alone, given as an uncompressed powder in small gelatin capsules (gr 1 each). As a routine, three grains were given each evening for 12 consecutive days, and patients remaining uncured by this treatment were given a double course of the drug (three grains daily for 24 days, 72 grains in all). Compressed pills or tablets coated with salol, keratin, or stearin were found to be unsatisfactory, for instance, after single courses of treatment there were 31 per cent failures with keratin-coated tablets compared with 8 per cent with the powder in gelatin capsules or cachets. In September 1918, the War Office Committee on Dysentery circulated recommendations, drawn up by Dobell and Dale, as to the treatment of patients infected with *E histolytica*, in the course of which it was stated that

'Emetine bismuthous iodide is an almost insoluble powder, from which emetine is gradually set free by contact with the intestinal juices. It is important, therefore, that such contact should in no way be prevented by the form of administration. The following procedures in dispensing have been shown to render the compound irregular in action or totally ineffective, and should be prohibited —

- (1) Compression of the powder into a hard tablet
- (2) The use of insoluble excipients, such as liquid paraffin, vaseline, or resin ointment. Soap has also proved unsuitable
- (3) Coating with keratin or stearin'

In the light of these experiences it is surprising to find that at the present day, as Manson-Bahr (1944) has pointed out, EBI is still being given very often in a form, such as keratin-coated tablets and compressed pills, from which it is not liberated. Bomford (1944) has ascribed recent failures to the use of keratin-coated capsules, which may not dissolve and have been recovered from the stools of patients. He found it necessary to crush the capsules and give them in a spoonful of jam. Dobell and O'Connor (1921) stipulated that the drug should be obtained from a trustworthy firm and be guaranteed to contain not less than 26 per cent of emetine. My experience during the past year has shown Martindale's 'slipules' of EBI to be satisfactory. Manson-Bahr's (1941) results demonstrate conclusively that EBI is effective when given in the form which Dobell (1918) advised, of 114 patients treated with total doses of 20 to 40 grains, he found that only 6 per cent relapsed.

Emetine compounds said to be less toxic than EBI have been introduced, emetine periodide (Martindale, 1923) and Auremetine, a combination of the hydriodide and periodides of emetine and the dye auramine (Willmore and

Martindale, 1926), but these have not been found to be as effective as EBI (Manson-Bahr, 1941)

Nausea and sometimes vomiting may follow the administration of EBI, and it is advisable that the patient should be in bed and only a very light diet be taken a few hours before the drug is given. The vomiting may occur very soon after the capsules have been swallowed, the red powder being returned, or 'therapeutic vomiting' due to release of emetine in the small intestine may occur after two to four hours. Manson-Bahr (1943) recommends that a sedative should be given half an hour before the EBI, for example phenobarbitone soluble gr 1, chloretone gr 10, or tincture of opium min 10 at 9.30 p.m. and EBI at 10 p.m. Efficient EBI treatment is followed by diarrhoea with dark brown or blackish stools.

*Toxic effects of emetine* The toxic effects which may possibly occur as a result of the administration of emetine and its compounds are far outweighed by the beneficial action of these drugs in amoebiasis. Alarming symptoms have been reported occasionally in some patients with an idiosyncrasy towards emetine, and as a result there has been a tendency to exaggerate its toxicity. Napier (1943) stated that while some adults would tolerate and feel better for 36 one-grain doses of emetine hydrochloride in as many days, many patients had been seriously disabled and yet others probably killed by a course of 12 grains in 12 days. On the other hand, Manson-Bahr (1941) found evidence of emetine intoxication in only seven of 259 patients who had undergone treatment with emetine injections. All of these seven patients had been subjected to prolonged courses of injections and had received total amounts ranging from 70 to 130 grains of emetine. Boyd (1945) has suggested that the toxicity of emetine may have been over-emphasized. He quoted his personal experience during the war of 1914-18, when he was given an injection of one grain of emetine daily for three months. During the last month of this treatment he was allowed up, having emetine in the morning and alcohol in the evening, with no ill effects. The most dangerous effect of emetine is on the heart, in which it may produce degenerative myocardial changes, with a fall of blood-pressure and alterations in conductivity, auricular fibrillation may occur (Sayid, 1935). According to Payne (1945), myocardial damage from excessive doses of emetine may be missed if the pulse is not examined after exercise. He considers that personal idiosyncrasy is an important factor. A falling blood-pressure is an early sign, and there may be alarming symptoms when the patient stands up, such as dyspnoea, cyanosis, and faintness. Craib (1945) has recorded the case of a nursing sister with amoebiasis who complained of exhaustion after her fourth injection of emetine. An electrocardiogram taken after the fifth injection revealed a flat T wave in lead I and an inverted P wave in lead II. The emetine was stopped, and two months elapsed before the electrocardiogram became normal. Emetine may also cause mental depression, peripheral neuritis, myositis (Young and Tudhope, 1926), desquamation of the skin, trophic changes in the nails with enlargement of the lunule, and diarrhoea.

The last may be confused with the diarrhoea produced by the dysenteric process. After a course of EBI, stiffness may persist in the legs for a considerable time (Manson-Bahr, 1943).

*The action of emetine* In 1928, Laidlaw, Dobell, and Bishop showed that a minute concentration of emetine, 1 in 5,000,000, was lethal for *E. histolytica* if it was in constant contact for a period of up to four days, provided that the medium did not become too acid. Their experiments showed that Boeck and Drbohlav's (1925) medium, consisting of solid and fluid, was quite unsuitable for testing the amoebicidal action of alkaloids. On incubation, a large but variable proportion of the emetine added to the serum passed into the coagulated egg, so that although a known amount of alkaloid might have been added to a given culture, the actual concentration present in the liquid, and acting upon the amoebae, rapidly became unknown and uncertain. They devised a medium of fluid only, and found that the reaction of the medium was important, as this affected the amoebicidal efficacy of the emetine. The final pH of the cultures was variable, and more regular results were obtained when the medium was buffered. The only possible fallacy remaining was the bacterial factor, which was not controllable. However, Dobell (1945) has been able to grow *E. histolytica* in culture with a single known strain of bacterium, and on repeating the original experiments with this extra precaution has confirmed his previous work. In fact, in these more rigidly controlled experiments, the amoebae appear to be if anything even more sensitive to emetine than was found originally. They are unable to survive for three or four days in concentrations of even less than 1 part of emetine hydrochloride in 5,000,000 at a pH of 7.2.

The reason for this lengthy consideration of emetine and its compounds is that this is the only anti-amoebic drug whose specific action on *E. histolytica* has been fully investigated and proved scientifically. As Adams (1944) has said, there is an urgent need for fundamental investigation in order to make the testing of new drugs in amoebiasis more scientific and less empirical than hitherto. Many other substances have been used in the treatment of amoebiasis and attempts have been made to find a drug which is as efficient as emetine and its compounds, but which is less toxic for the patient, but as yet this search has been without success.

*Iodine-oxyquinoline compounds* *Chiniofon* (B.P.) (*Yatren*, *Quinoxyl*, *Dysentalin*, *Anayodin*) This is a mixture of approximately four parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and one part of sodium bicarbonate. Muhlens and Menk introduced this drug in 1921 for the treatment of chronic amoebic dysentery and its sequelae. They reported that it had high bactericidal properties, and Vogel (1927) found that in a strong concentration (1 in 100) it had an amoebicidal action *in vitro*. It is a bright yellow powder containing some 28 per cent of combined iodine, and is exhibited in the form of pills and retention enemata. The pills contain four grains, and the usual dose for an adult is three to four pills thrice daily for 8 to 10 days, although Gunn (1931) recommended a course of 200 pills given

over a period of four to six weeks. The full dose may cause severe diarrhoea, and it is wise to begin with a small dose and increase gradually if this is well tolerated. Manson-Bahr (1943) has found that when given by mouth alone it fails to exterminate cysts. He noted on repeated sigmoidoscopic examinations that retention enemata of chiniofon exerted a direct effect upon ulceration in the sigmoid colon and in the lower part of the rectum, which showed rapid healing. The effects of chiniofon, given by the mouth and by the rectum simultaneously over a period of 10 days, were especially good in those cases which had become resistant to emetine and EBI, although the effects of the treatment were not always permanent (Manson-Bahr and Morris, 1925). As a result of this experience, Manson-Bahr decided to try the combined effect of EBI reinforced by chiniofon retention enemata, in view of the fact that chiniofon given rectally was particularly effective for lesions in the lower bowel, where it was improbable that EBI could exert full action. In his opinion (Manson-Bahr, 1943) this is the most efficacious form of treatment for intestinal amoebiasis yet devised. He usually gives two grains of EBI at night, preceded by a sedative, and a chiniofon retention enema during the day.

After a light breakfast at 8 a.m. the bowel is cleansed with an enema of 2 per cent sodium bicarbonate and at 8.30 a.m. a retention enema of 2½ per cent chiniofon in 7 oz. warm water is run in slowly through a number 10 rubber catheter with the patient on his left side and a pillow under the buttocks. He is then turned on to his back for half an hour, then on to his right side. The abdomen is massaged in an anti-clockwise direction. The foot of the bed is raised about 12 in. on blocks and the enema retained for eight hours. This is repeated on each morning for 10 days. It is recommended that if a relapse should occur after this treatment, the course should be repeated and the strength of the chiniofon retention enemata increased to 5 per cent.

The relapse rate within one year of treatment in a series of 361 patients was four per cent (Manson-Bahr, 1944), and this combined treatment is accepted by many physicians as the basis of their standard anti-amoebic treatment. Dobell, Gettings, Jepps, and Stephens's (1918) recommendations regarding EBI are followed by this author, a 12-day combined course being given, with a nightly dose of three grains of EBI (Martindale's sulpules, gr. 1 each). The strength of the chiniofon retention enemata may be increased to five per cent half-way through the course. Manson-Bahr (1944) insists that strict attention to the details as described is essential.

*Vioform* (iodochlorhydroxyquinoline) contains 37 to 41 per cent of iodine. It is given by the mouth in gelatine capsules containing four grains of the powder thrice daily for 10 days. David, Johnstone, Reed, and Leake (1933) considered it superior to chiniofon. The relapse rate of their cases was 23 per cent. Manson-Bahr's (1941) results were unsatisfactory, and all his cases relapsed. This compound is too irritant to be used for retention enemata.

*Diodoquin* (5,7-diiodo-8-hydroxyquinoline). This compound, which contains 64 per cent of iodine, is a tasteless and non-toxic drug which was first produced in America in 1935. Craig's (1937) report to the manufacturers

was most encouraging and both Silverman (1937) and Hummel (1939) published dramatic results, both claiming 100 per cent cures in series of patients treated with three tablets, gr 3 2 each, by mouth three times a day for 20 days. In 1940, Craig suggested that diodoquin might be of value in the prophylaxis of amoebic dysentery, seven tablets being taken daily for 20 days in endemic zones. Morton (1945) concluded that this drug appeared to be the best of the oxyquinoline group in the treatment of amoebiasis, being non-toxic and well tolerated in all but a small minority of cases, of the 78 patients whom he treated, two complained of mild pruritis ani and two developed abdominal pain and diarrhoea. His results, however, did not bear out the previous claims made for the drug. Approximately one-third of his cases had relapses at a preliminary stage, but he reported a dramatic clinical improvement in chronic cases of amoebic dysentery which previously had proved resistant to emetine, and he believed that diodoquin renders their entamoebae once more sensitive to emetine. He felt that the most useful role of diodoquin was its administration concurrently with emetine injections in amoebic hepatitis. He has used it in combination with chiniofon retention enemata and as a preliminary treatment before a 10-day combined course of EBI and chiniofon.

*Arsenical compounds* These have been used for many years in the treatment of amoebiasis. Salvarsan was recommended for amoebic dysentery in 1915 by Ravaut and Krolunitsky, who later (1917) gave it in conjunction with emetine. Other arsenical compounds were tried by French workers, and in 1923 Marchoux reported success with acetyl-oxy-amino-phenyl-arsonic acid (*Stovarsol*, *Acetarsol* (B P), *Spirocid*). In 1926, Dobell and Laidlaw found that the lethal dose of this compound for *E. histolytica in vitro* was about one-tenth of that of emetine. Given alone, it is not an effective drug—Manson-Bahr's (1941) relapse rate was 87.5 per cent—and it is now used mainly as an after-treatment in doses of 4-grain tablets twice daily by mouth for 10 days. Arsenical poisoning has sometimes followed its use, and occasionally a stovarsol rash may occur, an urticarial or rubelliform eruption on the face, neck, and trunk, which may be accompanied by pyrexia and glandular enlargement (Annesley, 1928, Manson-Bahr, 1943).

*Carbarsone* (4-carbamino-phenyl-arsonic acid) is allied to stovarsol. The same dosage is used, and it is said to be less toxic, although Epstein (1936) reported a fatal case of arsenical poisoning after its use. It was originally prepared by Ehrlich, and in 1931 Anderson and Reed in America found that it was effective in amoebic dysentery, in 1934, they reported 89 per cent cures with this drug alone. Mateer, Baltz, Marion, and Hollands (1940) reported 90 per cent cures with carbarsone alone, and 97 per cent when combined with retention enemata of chiniofon. Hummel (1939), however, reported 25 per cent failures with carbarsone alone, and Manson-Bahr (1941) reported 100 per cent failures. Morgan (1944) cited a patient who developed amoebic ulceration of the anal skin during carbarsone treatment, but was subsequently cured with emetine. Leishman and Kelsall (1944) have

found that it gives symptomatic relief in amoebic dysentery but is not curative, and in use it has been relegated by most British physicians to the same position as stovarsol. Both of these drugs have been given as retention enemata, 2 gm in 200 cc of warm sodium bicarbonate solution. Other arsenical preparations have been used in the treatment of amoebiasis, the most recent being *amibarson*, which is similar to carbarsone in composition and action (Chopra, Sen, and Sen, 1935).

**Bismuth salts** These have held a place in the treatment of amoebic dysentery for many years. They were strongly advocated by workers in Panama (Deeks, 1914, James and Deeks, 1925), who recommended large doses of bismuth subnitrate, 180 grains three-hourly in a tumblerful of milk or water, and found this effective either alone or with emetine. Bismuth subnitrate and bismuth carbonate are still used by some workers, usually combined with other anti-amoebic drugs (Adams, 1944), but there is no evidence that they have any specific action on *E. histolytica*. Manson-Bahr (1943) thought that they might merely mask the symptoms of an acute attack, or possibly render the contents of the colon incompatible to the parasite on account of the alkalinity produced.

**Other remedies** *Kurchi bark and its derivatives* The bark of *Hollarrhena anti-dysenterica* is an ancient Indian remedy for dysentery. It contains an alkaloid, conessine, which has been found to have some action upon *E. histolytica in vitro*. Kurchine hydrochloride has been used hypodermically and by mouth in doses of half to one grain, and kurchi bismuthous iodide was introduced by Acton and Chopra in 1933, given by mouth in doses of 10 grains. Chopra and Chopra (1942) have reported good results from the use of kurchi alkaloids in amoebic dysentery, but others have found them unsatisfactory (Manson-Bahr, 1943, Leishman and Kelsall, 1944, Hargreaves, 1944). Other native remedies are still used in some parts of the world, notably ya tan tsu (kho-sam), the seeds of *Brucea sumatrana*, in China (Liu, 1937, Wu, 1943), Chaparro Armagosa, an extract from the bark or leaves of the Mexican plant *Castela nicholsoni*, Simaruba, made from the bark of another plant of the same family as the previous two, Uzara, derived from an African plant of the family *Asclepiadaceae*, also Bael fruit. Bitter crystalline principles have been obtained from *Castela nicholsoni* and Simaruba, both of doubtful therapeutic action (Lillie and Shephard, 1917). Thorium salts, oil of chenopodium, adrenalin, benzyl benzoate, tannin, and iodoform are among numerous other substances which have been given by mouth in the treatment of amoebiasis, and also various medicated bowel washes have been used, for instance, rivanol, silver nitrate, eusol, iodoform, and mepacrine. Of the substances enumerated above, those generally in use today are emetine and its compounds, the iodine-oxyquinoline and arsenical compounds, and bismuth salts. At this stage, before proceeding to discuss the modern treatment of amoebiasis in more detail, it is worth reflecting on the lesions which *E. histolytica* produces in man and the many clinical manifestations which may result. It will be seen that each case of amoebic



dysentery must be regarded as a separate clinical problem, it is unlikely that any one drug alone will ever cure all cases, even though this drug be less toxic than emetine, more easily tolerated, and equally lethal towards *E histolytica*

### *Pathological and Clinical Considerations*

*E histolytica* is a tissue parasite which lives upon living tissues only, and apparently cannot nourish itself in any other way (Dobell and O'Connor, 1921). It normally lives at the expense of the tissues forming the wall of the intestine. The large intestine is its usual home, though it may attack the small intestine as well (Biggam, 1930), and it has been isolated from the duodenum (Wesemann, 1942). The amoebae erode or ulcerate the lining of the gut, and thus must always produce a more or less pathological state in the bowel of their host. The infected subject may be a healthy carrier and indistinguishable from a normal healthy person, or he may suffer from a fatal illness, and between these two extreme conditions all intermediate stages may occur. The use of the term cyst-carrier is to be deprecated, for every person who passes cysts must have vegetative amoebae living on the tissues of his bowel wall and completing their normal development. Most infected persons are healthy carriers and live with their parasites in a state of equilibrium, regeneration on the part of the tissues keeping pace with the cellular destruction brought about by the cytolytic ferment secreted by the amoebae. When this equilibrium does not exist or ceases, the superficial erosion of the bowel gives place to ulceration, the amoebae multiplying and passing more deeply into the tissues, breaking through the muscularis mucosae into the submucous layer, where they undermine the mucous membrane and produce characteristic 'button-hole' ulcers. These may coalesce and lead to large areas of ulceration, when secondary bacterial infection from the intestine occurs. In severe cases the muscular coat may be penetrated, giving rise either to perforation and general peritonitis or the formation of adhesions to neighbouring structures.

The liver of an infected person is always liable to attack by invading amoebae, as they may enter the blood-stream through eroded blood-vessels in the wall of the bowel and pass up through the portal vein to the liver, where hepatitis and liver abscess may result. Thus symptoms of amoebiasis of the liver may develop with or without intestinal symptoms or after they have subsided. From the liver the amoebae may pass into the systemic circulation and reach other organs, where they may colonize, for instance, the lungs or the brain. Amoebic abscesses of the brain have invariably proved fatal.

The symptomatology of intestinal amoebiasis is extremely variable, and almost any gastro-intestinal trouble may be simulated. The disease process in the bowel may be so acute that large portions of mucous membrane may become gangrenous and slough, but this is exceptional and even when dysenteric symptoms are present the patient may be leading an active life.

Cases of intestinal amoebiasis may be classified clinically as mild or latent forms, forms with acute onset, and advanced and chronic forms. Patients in the last category usually have recurrent bouts of diarrhoea with blood and mucus accompanied by colicky pain. The stools may be formed between the attacks though they also often contain some mucus and blood. Payne (1945) has recorded a fatal case with extensive ulceration without diarrhoea or obvious blood or mucus in the stools. There is often loss of weight and anaemia. Usually the caecum and descending colon, and often the liver edge, are palpable and tender. Intussusception has been reported (Parry, 1945). In severe chronic cases, there are often extensive adhesions and thickening of the bowel wall with narrowing of the lumen and occasionally tumour-like masses, 'amoebic granulomata' or 'amoebomata'. These changes (Morgan, 1944) are the result of repeated amoebic invasion of the bowel together with a superadded pyogenic infection, causing a progressive inflammatory lesion. The inflammatory process spreads through the bowel wall into the pericolic and perirectal tissues. The resulting area of thickening consists of fibrous tissue, overgrowth of granulation tissue, and varying degrees of ulceration. The wall of the gut is destroyed and small abscesses may be present in the centre of the mass. There is considerable round cell infiltration, lymphocytes and eosinophils are present in large numbers. Typical amoebic ulcers may be present, or on the other hand no evidence of amoebiasis may be forthcoming. In the latter case, it is likely that the parasites are dwelling in the depths of the gradually forming granuloma. The usual sites for such a process are the rectum, rectosigmoid junction, the colonic flexures, and caecum. When a local mass develops, the differential diagnosis from carcinoma is difficult and often impossible, even when it is within reach of the finger or the sigmoidoscope, and a biopsy may be necessary to exclude carcinoma even when amoebae are found in the stools, and carcinoma and amoeboma may co-exist. Sometimes in the early stages of amoeboma formation the whole mass may disappear after emetine treatment, but later, secondary infection, fibrosis, and colonic distortion may prevent this, and Morgan (1944) has found excision of the mass necessary on account of obstructive symptoms or because the exclusion of carcinoma is impossible.

Hummel (1939) stated that scarring and stricture formation in the upper rectum and colon may ensue as a result of secondary pyogenic infection. I have found two patients with rectal strictures in a series of 268 cases of chronic amoebiasis during the course of the past year. One of these patients required a temporary colostomy and excision of the stricture.

He was a sergeant-major aged 36 years who contracted amoebic dysentery in India in March 1944. In May 1944 a perirectal abscess developed. This burst into the rectum a month later and with the subsequent improvement in his general condition there was difficulty in defaecation, his faeces being shaped 'like a thin snake'. This difficulty increased, and he was invalided home. In May 1945, sigmoidoscopy revealed a fibrous sheet stretching across the upper part of the rectum, in the centre of which was a small round aperture less than 1 cm. in diameter.

*The Choice of Treatment*

The preceding brief account of the clinical and pathological aspects of amoebiasis cannot fail to emphasize the fact that early diagnosis and proper treatment are of the greatest importance in this disease, and that the longer the infection has lasted, especially if dysenteric symptoms have occurred, the more difficult is the cure. In an early case, the amoebae in the bowel wall may be comparatively easy of access for drugs, but later specific drugs may be prevented from reaching the amoebae as a result of local inflammatory changes, and there is little wonder that the treatment of chronic amoebiasis has proved a difficult problem. Again, it is very unlikely that any two cases of amoebiasis ever have identical lesions, so that no two series of cases can ever be strictly comparable.

Most authorities of the present day are agreed that the best chances of cure are held out by use of a combination of specific drugs. In spite of its unpleasant effects, EBI gr 3 given on 12 consecutive nights as a loose powder in gelatine capsules each containing gr 1, as recommended by Dobell, Gettings, Jepps, and Stephens (1918), appears to be the most effective basis of treatment. Daily retention enemata of chiniofon combined with this, as advocated by Manson-Bahr (1941), render the cure more certain. If there are dysenteric symptoms or if hepatitis is suspected, it is rational to precede this combined course with six daily hypodermic injections of emetine hydrochloride gr 1, which almost invariably give symptomatic relief. The patient should remain in bed throughout emetine and EBI treatment. As an after-treatment, it has been the custom of many physicians to give a course of one of the arsenical compounds, usually stovarsol or carbarsone, gr 4 twice daily for 10 to 12 days, but recent work suggests that a course of diodoquin, three tablets (gr 3.2 each) three times a day for 20 days, might be substituted for the arsenicals with benefit. The patient can be up and about during this after-treatment. The combined treatment as described above followed by a course of stovarsol was found last year to be more effective than a combined treatment in which for 21 days bismuth carbonate was given throughout, with auremetine gr 1 thrice daily on the odd days and chiniofon retention enemata and stovarsol gr 4 thrice daily on the even days. There were 15 per cent failures with the former course and 52.5 per cent failures with the latter (Hargreaves, 1945), which Lamb and Royston (1945) also found to be unsatisfactory. As has already been shown, several days continuous action of emetine is necessary to kill *E. histolytica* *in vitro*, and this is the rationale for giving daily doses of EBI.

Payne (1945), in two years' experience in Eastern India, found in treating primary cases that a course of treatment with 10 to 12 daily injections of emetine gr 1, followed by carbarsone 0.25 gm twice daily for 10 days, cured at the most only 50 per cent of the cases. Forty per cent of his patients passed cysts within three weeks after the end of the treatment, and although carbarsone cleared most of these, 10 per cent still needed more emetine or

a combined course of EBI and chiniofon. He reported that five per cent of his cases were resistant. His treatment was largely dictated by the drugs which were available, and he concluded that more thorough treatment of the initial attack with EBI and chiniofon retention enemata might reduce the number of chronic resistant cases. Sulphapyridine and sulphaguanidine given orally were found to relieve acute symptoms, but did not affect the amoebae. Marriott (1945) advised that in any particularly acute case of dysentery where *E. histolytica* is identified, a course of sulphaguanidine should be given while emetine injections are being administered. He stated that bacillary and amoebic infections often co-exist, and any very acute attack of dysentery should be suspected as being possibly bacillary dysentery affecting a patient harbouring amoebae.

As the result of his recent work with diodoquin, Morton (1945) has suggested that a course of treatment with six injections of emetine hydrochloride together with three tablets of this drug by mouth thrice daily for 20 days should be tried in primary amoebiasis overseas, and that a controlled series of patients should be compared with a similar series treated with emetine, EBI and chiniofon. In my experience, a 20-day course of diodoquin has at times proved effective in clearing healthy carriers who have had to be treated as ambulant cases.

#### *Refractory Cases of Chronic Amoebic Dysentery*

The treatment of an early case of amoebic dysentery is by no means speedy, taking some five or six weeks if the patient is to be given every chance of a cure, but the chronic case presents a far more complex and difficult problem. Some of the men who arrived home last year had been under almost continuous treatment for two years without success. Many were wasted and bedridden with persistent foul diarrhoea. Their stools contained much blood and mucus and many amoebae. Some of these men had been given standard courses of combined treatment from the start, although the EBI had been given in pills or compressed tablets, but the usual story was one of repeated courses of emetine injections. As already stated, the history of many of the worst cases dated from the fall of Burma in 1942, when chaos reigned. These men were amongst the survivors of the long escape route back into India, during which time many were without food, and dysentery and malaria were rife. When eventually these men reached their goal, often several weeks after the onset of dysentery, there were not sufficient drugs available for effective anti-amoebic treatment, and indeed some of them had to attend as out-patients for emetine injections at hospitals which were already overflowing with patients (Hargreaves, 1945). EBI was often unobtainable then, and it was seldom available in India during the next year. Leishman and Kelsall (1944) found that when a supply of the drug was obtained it did not help their chronic cases, but they did not state the form in which it was given. Thus in many of these chronic

cases there was a delay before initial treatment could be obtained, and when eventually this was available it was usually inadequate. When the men reached hospital in this country, only a proportion of them were cured after repeated and intensive courses of combined treatment, the residue remaining infected despite any course of anti-amoebic treatment which could be devised. Adams (1944) has suggested two explanations for the intractability of the infections. Either the men were infected with an unusually virulent and resistant parasite or, as he thought, their parasites had become resistant to the action of emetine as the result of excessive dosage with the drug long after it should have been plainly evident that it was not effective. He has also suggested that an infection made resistant to emetine is less amenable to any other available drugs. Manson-Bahr (1944) also considers that in this way *E. histolytica* may be made emetine-fast, as, in his experience, previous intensive emetine treatment has rendered the disease more difficult to eradicate. He has recently had success in his refractory cases as the result of preceding anti-amoebic treatment by protein shock therapy, given with the idea of desensitizing them.

*The question of virulence.* As regards the theory that the refractory cases from Burma and India were infected with an unusually virulent strain of amoebae, full discussion on the question of the pathogenicity of various strains is beyond the scope of the present paper. The position is far from clear (Hoare, 1944) and needs further investigation, especially as regards the theory that there are two main varieties of *E. histolytica*, large and small, and that amoebae of the small variety are non-pathogenic to man. No work has yet been done to disprove the work of Walker (1911) and Walker and Sellards (1913) who showed that the susceptibility of man is a more important factor than any variation in the virulence of the amoebae in determining the pathogenicity of *E. histolytica*. This probably depends to some extent upon the environment which the amoebae find in the intestine. There has been no report of any cases occurring in this country amongst the contacts with repatriates from Burma and India, and such might surely have been expected if these men were infected with particularly virulent strains of amoebae. Westphal (1938) and Deschiens (1939) believed that the flora associated with the amoebae are important in determining its pathogenicity. The former's conclusion was based upon an experiment in which he himself swallowed washed cysts of *E. histolytica*, after which he passed numerous vegetative forms and cysts without suffering from symptoms. Eight months later, he and a friend each drank a suspension of amoebic dysentery stool which was said to contain no cysts. They both had symptoms of colitis after this, but whereas his friend soon recovered, Westphal himself developed amoebic dysentery a month later. It is difficult to understand how any useful conclusion could have been drawn from such a crude experiment.

*Emetine-resistance.* During the war of 1914-18 it was often suggested that cases which had been previously treated with emetine were for that reason

more difficult to cure with the double iodide than those to whom no emetine had previously been administered, and that repeated injections of emetine might render the parasites emetine-resistant. Dobell, Gettings, Jepps, and Stephens (1918) could not support these suggestions, many of the patients whom they cured with a single course of EBI had had previous courses of treatment with emetine injections. One patient had had 100 injections, whilst one of the failures had never been treated with emetine in any form. Again, in the war of 1939-45, chronic refractory cases have been labelled emetine-resistant, on account of the indiscriminate administration of courses of emetine injections. The work of Halawani (1930) and Bonnin and Aretas (1938) has been accepted by some authorities as proving that emetine-resistant amoebae can be produced experimentally *in vitro*. Halawani's conclusions, however, as regards emetine-resistance *in vitro*, were entirely unjustified, because the methods used were so fallacious that no conclusion at all could be drawn from his experiments. Firstly, he used a solid-liquid medium with which the experimental error is greater than the effects supposed to be produced. As explained above, this was shown by Laidlaw, Dobell, and Bishop (1928) two years before Halawani's work appeared, and he ignored this. Secondly, he also used a liquid medium consisting of dilute egg-white in Ringer's solution. According to Dobell (1945), *E. histolytica* cannot be cultivated in this at all. The amoebae can merely survive in it for variable times, depending upon the pH, the bacterial flora, and other factors, all of which Halawani ignored. Bonnin and Aretas (1938) also claimed to have produced emetine-resistant strains of *E. histolytica* *in vitro*. Their methods were similar to those used by Halawani, and their conclusions are therefore open to the same criticisms. They again made no reference to the work of Laidlaw, Dobell, and Bishop (1928). In all attempts by Dobell (1945) to produce emetine-resistant strains of *E. histolytica* by growing amoebae in media containing the alkaloid, the results have been negative.

*Secondary bacterial infection.* The important part played by bacteria in preventing a response to anti-amoebic treatment was again emphasized in May 1944 by the post-mortem findings when a patient died in spite of repeated courses of standard treatment. This was at a Military Hospital which was a special centre for intractable cases of chronic amoebic dysentery (Hargreaves, 1944, 1945). The peritoneal cavity contained turbid fluid and there were many adhesions and loculi of thick pus. The wall of the lower part of the ileum and the whole of the large bowel was dark in colour, thickened, and rigid, and the mucous membrane was necrotic. In places the necrotic processes extended deeply into the muscular layer of the wall and many perforations were found, some being sealed off by the omentum.

At that time another patient in the same hospital appeared to be moribund. This man had been invalided from India, where he had been under almost continuous treatment for amoebic dysentery since 1942. He had arrived home in December 1943, and four months later, as there had been

no response to two courses of anti-amoebic treatment, he was transferred to the special centre, where he continued to go downhill in spite of treatment. He was cachectic and pyrexial with persistent abdominal pain and was passing some 20 foul stools daily, containing blood and many amoebae. His colon was exquisitely tender and appeared to be thickened throughout its length. There was a leucocytosis of over 20,000 cells per c mm. Sigmoidoscopy was impossible owing to pain, but the lower part of the rectum was seen to be severely ulcerated, the intervening areas of mucous membrane being injected and oedematous. He was not considered fit to stand an operation for ileostomy and needed repeated administrations of morphia to relieve his pain. Penicillin was available then for special cases, and it was decided to try this as a last resort. The patient was given an initial dose of 100,000 units intramuscularly followed by 33,000 units three-hourly, up to a total of just over 1,000,000 units. The result was dramatic, 24 hours after starting the treatment he was free from pain and apyrexial, and after two days he passed a normally formed stool. He rapidly put on weight, but amoebae were still present in the stools, and after two weeks there was a recurrence of diarrhoea with blood. He was then given another course of penicillin, this time a total of 2,250,000 units, and again his symptoms subsided and his lower bowel was found to be healthy on sigmoidoscopy. His stools still contained amoebae, and he was given a standard course of anti-amoebic treatment. Four months later, he was well and free from symptoms. Six daily examinations of the stools were negative, and sigmoidoscopy was normal. This man's life was undoubtedly saved by penicillin, which was given subsequently to 47 other severe cases with good results, in courses of 2,000,000 units, 100,000 units initially, followed by 33,000 units three-hourly. Willmore (1944) has also found penicillin to be beneficial in chronic amoebic dysentery, improving the clinical condition dramatically.

Any of the bacteria normally present in the lumen of the bowel may gain access into the bowel wall through the ulcerated mucosa, including numerous strains of streptococci and staphylococci which are penicillin sensitive. With the object of combating some of the organisms which are not sensitive to penicillin, succinyl sulphathiazole (sulfasuxidine) is now given concurrently by the mouth. Mackenzie's (1944) work with this drug has shown that a dosage of 20 gm daily is most effective in reducing the Gram-negative organisms in the stools. Neither penicillin nor sulfasuxidine has been found to have any appreciable effect on *E. histolytica*, but repeated sigmoidoscopic examinations during this treatment have shown that improvement occurs in the condition of the bowel. The oedema and hyperaemia of the mucous membrane is seen to subside, with the result that the ulcers become more superficial in appearance, and healing often begins before specific anti-amoebic treatment is given. After this preliminary treatment, only occasionally have more than one combined course of EBI and chiniofon retention enemata been necessary to clear the amoebic infection, and no clinical evidence of emetine-resistance has been found. Some cases needed more

than one course of penicillin and sulfasuxidine for example, one patient with multiple perirectal abscesses and another who had a large hard craggy tumour in the region of the splenic flexure. In the latter patient a large filling defect was demonstrated radiographically, and carcinoma of the colon was suspected. The tumour showed no response to treatment with emetine injections, but when these were repeated after two courses of penicillin the mass disappeared completely. Before the days of penicillin it would have been necessary to excise this tumour.

*Surgery* This recent advance in treatment should thus obviate the necessity for surgical operations in many cases where hitherto they would have been unavoidable, and drastic procedures such as ileostomy, appendicostomy, and caecostomy, which have sometimes been used in the past as a last resort for severe cases of chronic amoebic dysentery, should not be necessary. If local tumours persist in spite of treatment with penicillin and emetine, surgery should not be delayed. Morgan (1944) removed a caecal mass from a patient with chronic amoebiasis, and even after removal the tumour was thought to be an amoeboma, but microscopic examination revealed that it was an adenocarcinoma. Incidentally, many cases of amoebiasis have been operated upon mistakenly for appendicitis. In one of the Chicago epidemics appendicectomy was performed in 32 cases, of which 13 died (Strong, 1945). Payne (1945) recorded two cases of amoebic typhlitis which were opened under the impression that they were suffering from appendicitis, and at operation plastic peritonitis was found.

The idea of attacking bacterial invaders in this disease is by no means new. For instance, medicated bowel washes and retention enemata have been in use for many years, and the iodine-oxyquinoline group of drugs in particular have a bactericidal effect by virtue of their high iodine content. Again, Acton and Knowles (1928) and Napier (1943) advocated the use of vaccines prepared from organisms isolated from the stools and obtained from ulcers by means of the sigmoidoscope, holding that if secondary bacterial infection were overcome the tissues were better able to deal with the amoebic infection. The dramatic response shown by chronic refractory cases to modern antibacterial agents, and their subsequent cure by standard anti-amoebic treatment, leaves little doubt that as the result of the elimination of secondary infection the amoebae become easier of access for specific drugs.

*Sigmoidoscopy* The sigmoidoscope is of most value in the diagnosis of amoebiasis, but it is also a useful guide in the treatment of cases with ulceration within its reach. As already shown, the lesions can be seen to change considerably during treatment. Manson-Bahr (1943) has found epithelialization to occur within 12 days from the start of his combined treatment. The knee-chest position is easiest for the operator, but if the patient is too ill to maintain this the lateral position is usually employed. In patients with severe ulceration, proctoscopy may be sufficient, 50 per cent of all cases show lesions in the rectal ampulla (Payne, 1945). Sigmoidoscopy should always be preceded by digital examination of the rectum. If this is



not done, palpable carcinomata may be missed, as superficially they may resemble amoebic lesions. Again, infiltrated malignant glands may sometimes be felt through the rectum when no visible lesion can be detected (Manson-Bahr, 1943)

### *General Treatment*

If the patient has severe dysenteric symptoms, a fluid diet only may be tolerated, but it is generally agreed that as soon as possible a high calorie diet should be given. Payne (1945) found that diet made very little difference and that the maintenance of good nutrition and attention to the vitamin intake, especially the B group, was more important than the need for a low residue diet. Sometimes the intravenous administration of salines, plasma, or blood may be indicated. Thurston (1945) has seen oedema of the legs and ascites occur as the result of hypoproteinaemia in chronic cases in India. Many patients have arrived back in England emaciated and in some cases very short of vitamins, and some have had symptoms and signs of beri-beri (Priest, 1944). Ruffin (1943) advised a well-balanced diet supplemented by large doses of nicotinic acid, thiamine, and riboflavin. Great patience has to be exercised in treating cases of chronic amoebic dysentery. A cheerful ward sister is a great boon as, psychologically, men who have been in hospital continuously for many months and had repeated courses of treatment without success tend to reach a pathetic state of depression and to give up hope. All treatments must be strictly supervised, especially the administration of EBI on account of its unpleasant effects.

*Post-dysenteric symptoms* After severe amoebic dysentery it is often found that residual intestinal symptoms may persist for several months. At sigmoidoscopy on the completion of treatment the colon frequently shows a tendency to spasm, and there may be symptoms of a brisk gastrocolic reflex. Such symptoms are often benefited by the administration of a pill containing dry extract of belladonna gr  $\frac{1}{4}$  and codeine sulphate gr  $\frac{1}{2}$  after breakfast. Sometimes obstinate constipation may occur, and this can usually be relieved by liquid paraffin or agar emulsion.

### *Tests of Cure*

Dobell's (1917) investigations show that negative protozoological examinations of the stools made during the course of treatment are practically worthless as evidence of non-infection. To prove that an infection has been removed by treatment it is necessary to make at least six negative examinations covering a period of at least three weeks after the end of the treatment. These requirements represent an absolute minimum. In 1918 the War Office Committee on Dysentery recommended one stool examination in the first week after treatment, one (or two) in the second week, and four (or three) in the third week. It was also recommended that whenever possible each case should be examined by the same protozoologist or protozoologists.

throughout To be more certain of a cure having been effected it is necessary to exceed this minimum (Dobell and O'Connor, 1921) The routine tests of cure now recommended for chronic cases are as follows (Hargreaves, 1945) In the second week after treatment three daily specimens of stools are examined and sigmoidoscopy performed If these tests are satisfactory, the patient is sent away for a month's convalescence, after which he is readmitted to hospital, provided there has been no return of symptoms, in which case he returns immediately After readmission six further daily stools are examined and sigmoidoscopy is repeated

### *Enemy Propaganda*

It is interesting to note that in the recent war the Germans have also realized that amoebic dysentery is a disease fraught with difficulties In the Central Mediterranean theatre (Boland, 1945) enemy propaganda leaflets were showered upon our troops from the air, and this was one of the conditions which they were urged to simulate in order to be admitted to hospital for long spells and thus to avoid fighting The pamphlet in question reads thus —

#### ‘WORLD WAR NO 2 IS ALMOST OVER

‘Nobody can say that as a good soldier you haven't done your duty But no man in the world will ever blame you for not wishing to be one of its last victims It is far better for you to be a few weeks ill than all your life dead You don't know how to do it? Well, we're going to teach you the “rules of the game”

‘1 The doctor should feel straight away “Here is a good soldier who has the misfortune of being ill against his will” Therefore you shouldn't exaggerate your illness

‘2 Make up your mind for one kind of disease and stick to it

‘3 Above all you mustn't tell the doctor the name of the disease you pretend to be suffering from Don't use any technical terms, doctors don't like that You will never be found out if you say too little, but you might easily be caught if you say too much

‘Never forget Better a few weeks ill than all your life dead

#### *‘Dysentery*

‘Take a laxative, preferably castor oil (In Italian *Olio di ricini*) When it has begun to work report to your doctor with the following complaints Tell him that you had a severe attack of dysentery some months ago in Africa, South Italy or some such place with slime and blood in your motions Since that time you notice that heavy foods, such as pork and beans, fat meats, etc., produce violent pains in your stomach and diarrhoea Occasionally your motions have been slimy with red streaks and lumps in them Tell the doctor that you nearly always suffer from mild gnawing pains in your abdomen high up, especially on the right side, but sometimes also lower down on the left side Say that you feel weak and run down

'When the doctor examines you show painful response to pressure on the right side immediately below the ribs, also during examination of the right kidney

'Stick to your story at the hospital and don't forget to take a laxative from time to time

'A few weeks after leaving hospital you might try the whole thing again'

### Conclusions

If chronic amoebic dysentery is to be prevented, early diagnosis and efficient treatment of amoebiasis are essential. In many of the distressing cases of chronic amoebic dysentery invalided home during the war of 1939-45 there was unavoidable delay in treatment, and when eventually this was available it was unsatisfactory.

Emetine is the most effective amoebicidal drug known at present. An infinitesimal concentration of this alkaloid is lethal for *E. histolytica* *in vitro* if it is in constant contact for up to four days at a pH of 7.2. Many other substances have been advocated as being specific for amoebiasis, but these have mostly been used on empirical grounds only, and there is an obvious need for more scientific testing of new remedies by expert protozoologists.

Emetine injections are specific for amoebiasis of the liver, but contrary to widespread belief, they cure only a small percentage of cases of amoebic dysentery. For this, EBI is the most efficient basis of specific treatment, if given as a loose powder in gelatin capsules, gr. 3 nightly for 12 consecutive nights. Unfortunately it is still being dispensed in compressed pills and tablets, although these were shown in 1918 to be unsatisfactory.

The chances of cure are increased if daily retention enemata of chiniofon are combined with the course of EBI. The iodine-oxyquinoline compounds, of which chiniofon is one, were introduced as the result of a search to find a more pleasant substitute for EBI. As well as having a mild amoebicidal action, these compounds exert a bactericidal effect upon secondarily infecting organisms. Diodoquin, the most recent of these drugs to be evolved, appears to be the most potent of them by the mouth, and a course of treatment with this substance, three tablets thrice daily for 20 days, is useful as an after-treatment following EBI and chiniofon, and can be taken during convalescence. Stovarsol and carbarsone have formerly been given in after-treatment, but they are not considered to be as effective as diodoquin.

Injections of emetine hydrochloride control acute dysenteric symptoms, and should be given before the combined course in early cases with such symptoms. Not more than six daily injections of gr. 1 should be necessary, and at the same time it is rational to give sulphaguanidine or sulfasuxidine by the mouth in order to combat bacterial infection.

Secondary bacterial infection has been found to be an important factor in severe refractory cases, and the use of penicillin has proved life-saving. An attack on invading bacteria with penicillin and sulfasuxidine produces

a dramatic improvement in these cases and makes them more amenable to specific anti-amoebic treatment. Chronic cases previously labelled emetine-resistant have been cleared of their infection by standard treatment with EBI and chiniofon retention enemata, when this has been preceded by penicillin parenterally and sulfasuxidine by mouth. There is as yet no scientific proof that emetine-resistant strains of *E. histolytica* exist or can be produced.

Each case of amoebic dysentery is a separate clinical problem, and the sigmoidoscope is a most valuable guide to treatment. Radiography may also be useful in this respect, for instance, in cases with amoebic granulomata. Repeated courses of penicillin may be necessary in particularly severe cases with these tumours or with pericolic or perirectal abscesses. The need for surgical interference has been diminished as the result of this new approach to treatment.

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## PAMAQUIN HAEMOGLOBINURIA<sup>1</sup>

BY S B DIMSON AND R B McMARTIN

### *Introduction*

SINCE the use of pamaquin (plasmoquine) as an antimalarial drug, attacks of haemoglobinuria attributable to its use have been described. With its routine adoption by the Army such attacks have become more frequent. The experience of an Indian General Hospital (Combined) when in Ranchi (Bihar) in 1943 may be given as an example. During the whole of 1943, among 12,000 Indian malaria patients seven instances of haemoglobinuria developing with pamaquin occurred, one during routine malarial treatment and six after 'blanket treatment'.

The colloquial expression 'blanket treatment' is used to describe a course of treatment given to men withdrawn from a malarious area to one which is non-malarious, on the assumption that they have already developed sub-clinical malaria.

The standard Army treatment for malaria at that time was quinine gr 10 tds for two days, mepacrine 0.1 gm tds for five days, rest for two days, pamaquin 0.01 gm for five days, bd for Indian troops and tds for British. 'Blanket treatment' consisted of mepacrine 0.1 gm tds for five days, rest for two days, and pamaquin 0.01 gm for three days, irrespective of race. It was given when suppressive mepacrine, 0.1 gm daily, was discontinued. The cases to be described occurred on the Arakan-Burma frontier in 1944. Out of about 10,000 Indian troops who received 'blanket treatment' on taking up monsoon quarters, the majority receiving pamaquin for five days instead of three, 13 developed haemoglobinuria while on pamaquin, and were admitted to our hospital. Most of these patients were Punjabis, and three of them died. By contrast, among the much smaller number of British troops who received 'blanket treatment' at the same time none developed haemoglobinuria. A further five cases among 10,000 Indian troops developed the condition here while undergoing the routine Army treatment for malaria.

### *Clinical Findings*

It will be seen from Table I that haemoglobinuria was observed after doses of pamaquin varying from 0.03 to 0.15 gm. The onset was gradual in most cases. The condition took one or two days to develop fully, the first sign being a gradual darkening in the colour of the urine. Rigors occurred only when the onset was sudden. Fever, epigastric pain, persistent bilious vomiting,

<sup>1</sup> Received August 5, 1945



## Aetiological Factors

Case	Date of admission	Home province	Arakan service, months	Suppressive mepacrine, months	'Blanket' treatment, given	If on duty	Dose of pamaquin before haemoglobinuria	Malaria history	Blood film	Size of spleen F = finger	Remarks
1	7 8 44	Punjab	6	12 irregularly	Yes	Yes	0.09 gm	Irregular attacks of fever	Neg	Not felt	—
2	3 7 44	Punjab	5	2 regularly	Yes	Yes	0.06 gm	1939, once	Neg	Not felt	—
3	31 7 44	Punjab	9	9 regularly	Yes	Yes	0.06 gm	1939, once	Neg	1 F	—
4	2 8 44	Punjab	9	3 regularly	Yes	Ex-cused	0.06 gm	1943, once	M T 2 days later	Not felt	—
5	3 8 44	Punjab	10	18 regularly	Yes	Yes	0.09 gm	Nil	Neg	Not felt	—
6	3 8 44	Punjab	18	18 regularly	Yes	Yes	0.03 gm	Nil	Neg	1 F	—
7	2 8 44	Punjab	6	4 regularly	Yes	Yes	0.09 gm	Nil	M T	Not felt	—
8	9 8 44	Punjab	3	3 regularly	Yes	Yes	0.09 gm	Nil	Neg	Not felt	—
9	27 7 44	Hyderabad	21	21 irregularly	Yes	Yes	0.15 gm	1942, once	Neg	Not felt	—
10	26 8 44	Bengal	2	7 2	?	Yes	?	Nil	Neg	2 F	—
11	26 7 44	Punjab	5	5 regularly	Yes	?	0.03 gm	?	M T	Not felt	—
12	7 8 44	Punjab	3	3 regularly	Yes	Yes	0.09 gm	Nil	Neg	3 F	Died
13	28 7 44	?	10	10 regularly	Yes	?	0.15 gm	Nil	Neg	2 F	Died
14	10 4 44	Bengal	?	Nil	No	No	0.08 gm	?	Treated for clinical malaria	3 F	—
15	17 6 44	Bengal	9	Nil	No	No	0.08 gm	6 months ago	Treated for M T malaria	Not felt	Quinine haemoglobinuria 3 years previously
16	26 7 44	Kashmir	1	1 regularly	No	No	0.10 gm	Nil	Treated for clinical malaria	1 F	—
17	2 8 44	Punjab	8	Nil	No	No	0.10 gm	Nil	Treated for clinical malaria	Not felt	—
18	20 9 44	Punjab	10	1 regularly	No	No	0.10 gm	1 month ago	Treated for clinical malaria	1 F	—

thirst, prostration, generalized aches, reddish-black urine, and jaundice were the usual symptoms. Anaemia with jaundice was generally well marked, and the tongue, dry and coated, indicated dehydration. The liver area was tender and the spleen was enlarged from one to three fingers in nine cases. Fever was irregular and protracted, lasting on the average 10 days. In one case it was present for one day only and in another lasted one month. The pulse was rapid, thin, and of low tension. When recorded soon after the onset of haemoglobinuria, the blood-pressure was low. The average systolic pressure was 105 mm and the average diastolic pressure 45 mm, but in two cases the diastolic pressure was temporarily zero. In these two cases cyanosis and dyspnoea co-existed. Cyanosis was present in five patients, most of whom were severely ill. In the serious cases there was an anxious facies and a restless behaviour which in two instances went on to a toxic confusional state, ending fatally.

One typical example, Case 12, may be given. This patient had received nine tablets of pamaquin during 'blanket treatment' while on full duty when he complained of giddiness and weakness with, next day, black urine, jaundice, and vomiting. On admission, cyanosis and anaemia were present (red cells 3,500,000 per c mm and haemoglobin 11.9 gm per 100 c c). The right hypochondrium was tender, the spleen was enlarged two fingers, and methaemalbuminaemia and methaemoglobinuria were present. The apex beat was forceful one inch outside the mid-clavicular line in the fifth space, with a systolic murmur. The blood-pressure was 120/40, temperature 102° F, pulse 120, and respirations 28. Urinary output was good throughout. Coma and intense dyspnoea supervened two days later, with red cells 900,000 per c mm, haemoglobin 5 gm per 100 c c, van den Bergh units 16, and blood-urea 90 mg per 100 c c. Although the apex beat was strong, the pulse was feeble and the skin cold. The urine was clear by this time. He died three days after admission from circulatory failure after repeated haemolysis. At post-mortem, performed within six hours of death, the body was seen to be that of a poorly nourished man of 25 years with brownish-yellow staining of his tissues, which were grossly anaemic. The brain was congested with excess of brownish cerebrospinal fluid. The myocardium was flabby and pale, and pericardial fluid was in excess and brownish in colour. The lungs were intensely congested, with dense pleural adhesions on the left side. Blood-stained froth was present in the bronchi. The liver was slightly enlarged and pale chocolate in colour. The spleen was enlarged three times, was magenta in colour, and malpighian follicles were not visible. No malarial parasites were seen. The kidneys were very congested. Sections of liver, spleen, kidneys, brain, and adrenals were sent for examination. Post-mortem findings in the remaining two fatal cases were similar and likewise characteristic of those described in classical blackwater fever. Death in one was due to repeated haemolysis and circulatory failure and in the other to uraemia.

*Differential diagnosis* Half the number of cases sent into hospital for admission were labelled jaundice or infective hepatitis. This error need not

have arisen because the appearance of the patient and the colour of his urine were characteristic. Canary-yellow conjunctivae, together with anaemia, prostration, and a reddish-black urine made the clinical picture of haemoglobinuria easy of recognition. The other disease in the Arakan which might have caused confusion in diagnosis was malignant tertian malaria with jaundice (bilious remittent fever). In malaria the patient looks heavy-eyed and tired more often than prostrate and anxious, the anaemia is usually much less severe, and malarial parasites are almost always found in the blood. Urine examination was pathognomonic, showing the combination in a dark red urine of the absence of red cells with positive occult blood tests and the presence of oxyhaemoglobin and/or methaemoglobin. It was more difficult to decide if the haemoglobinuria was a phenomenon due entirely to pamaquin toxicity or if the cases here described were essentially classical blackwater fever cases precipitated by pamaquin. Amy (1934) asserted that the conditions, though allied, could be differentiated by the presence of cyanosis and intracorpuseular methaemoglobin in pamaquin haemoglobinuria. The reason for his view was that a common toxic effect of pamaquin is cyanosis, generally attributable to the formation of intracorpuseular methaemoglobin. He recorded cyanosis, however, in only four of 11 cases of pamaquin haemoglobinuria (Amy, 1934, 1935). It was present in only five of the 18 cases in our series. In classical blackwater fever cyanosis was present in three out of nine cases described by Fairley and Bromfield (1934). It is therefore evident that cyanosis can occur in both conditions which clinically are identical, and is of no help in differential diagnosis. Amy's assumption, without spectroscopic evidence, that intracorpuseular methaemoglobin is the cause of the cyanosis seen in pamaquin haemoglobinuria is purely theoretical and is probably incorrect, for the following reasons. No methaemoglobin was seen in the laked red cells of our pamaquin haemoglobinuria cases even when cyanotic, and 50 ordinary malaria patients used as controls after a full course of 0.1 gm. pamaquin did not show intracorpuseular methaemoglobin in their blood, whereas most patients in the present series developed haemoglobinuria on a dosage smaller than this. Amy's view is upheld by many authorities who go on to infer without experimental proof that when intracorpuseular methaemoglobin causing cyanosis is produced in excess, haemoglobinuria results. We believe this view to be mistaken, and regard haemoglobinuria to be as unrelated to cyanosis as haemolytic anaemia after sulphapyridine is to the cyanosis it so commonly produces. It is more probable that the cyanosis seen was due either to increased production of methaemalbumin in the plasma due to repeated haemolysis, or to the circulatory failure which occurred in the severe cases, or to a combination of both factors.

#### *Treatment*

All patients were kept at absolute rest in bed, fluid intake and output charted, and fluids given to the limit of tolerance. Where oral administration was hindered by excessive vomiting, glucose-saline was given by intravenous

drip and *per rectum*. This was necessary in nine cases. An alkali mixture containing 20 gr each of sodium citrate and sodium bicarbonate was given every two hours and was usually retained. It was discontinued when the urine remained clear for over two days. Blood transfusions were not given because of the impossibility of obtaining donors quickly. Anti-venom serum (Cobra and Russell's Viper, concentrated, Kasauli) was added to the drip in five cases, one of which died five hours after admission. The dosage was 20 c.c. initially and 10 c.c. every four hours up to a total of 50 to 70 c.c. This treatment, advocated by Inder Singh and Inderjit Singh (1944), is not a new one. Conflicting reports regarding its value were recorded by Ross (1932). No conclusion as to its efficacy can be drawn from the results of our small series.

### *Laboratory Findings*

*Urine* The colour varied between a port-wine and a reddish-black colour. In some cases it was impossible to distinguish by colour alone between the blood and the urine. Albumin, casts, debris, and excess of urobilinogen were present. The reaction was alkaline in two-thirds of the cases. Spectroscopy showed that in the acid urines, in addition to oxyhaemoglobin, methaemoglobin was present, identified by its characteristic  $\alpha$  band. Oxyhaemoglobin was also present in the alkaline urines, but it was more difficult to decide if alkaline methaemoglobin was present as well, since its  $\alpha$  band is generally too faint to be seen. In one alkaline urine examined within five minutes of being passed the  $\alpha$  band of alkaline methaemoglobin was quite distinct, presumably due to the large amount which must have been present. Some of these urines were acidified with dilute acetic acid, but the  $\alpha$  band of methaemoglobin could not be seen. The haemoglobinuria took two to five days to disappear.

*Blood* For details of blood examinations Table II should be consulted.

The colour was usually dirty brown, but sometimes almost black, the corpuscular and plasma layers being then indistinguishable.

Spectroscopy showed the presence in the plasma of methaemalbumin instead of methaemoglobin, which calls for comment. Farley (1941) has shown that the pigment resulting from intravascular haemolysis, formerly supposed to be methaemoglobin, is in reality methaemalbumin formed by the combination in the plasma of haematin (ferric) with serum albumin. With a hand Beck spectroscope it is impossible to differentiate the  $\alpha$  band of methaemoglobin (630  $\mu\mu$ ) from that of methaemalbumin (623  $\mu\mu$ ) by direct spectroscopy. The theoretical possibility exists that in pamaquin haemoglobinuria both pigments could be present in the plasma. Reagents which disperse the  $\alpha$  band of methaemoglobin were therefore added to the plasma in two cases. Hydrogen peroxide 10 vols in one instance and 10 per cent ammonium sulphide in another caused neither disappearance nor lessening in density of the  $\alpha$  band seen. This made it very unlikely that intracorporeal methaemoglobin due to pamaquin had been liberated in any appreciable

TABLE II  
Results of Blood Examinations

Case	Interval, days after onset	Plasma				Blood			
		Methaemalbumin	Specific gravity	Protein gm per 100 cc	van den Bergh units	Specific gravity	R B C millions per c mm	Hb gm per 100 cc (Sahli)	Urea mg per 100 cc
1	1	Present	1 024	5 83	—	1 044	1 91	8 0	40
	16	Neg	1 025	6 17	—	1 049	4 00	11 3	—
	27	Neg	1 028	7 20	—	—	—	14 5	—
	34	—	1 026	6 52	—	—	—	—	—
2	1	Present	1 029	7 55	—	1 043	2 39	7 7	60
	2	Present	1 035	9 60	—	1 043	1 35	5 6	—
	7	Neg	1 025	6 17	2 0	—	—	4 5	140
	38	—	1 026	6 52	—	—	—	—	—
3	0	Present	1 027	6 86	—	1 045	2 61	7 7	60
	10	Neg	1 025	6 17	0 4	—	—	—	36
	30	—	1 028	7 20	—	—	—	—	—
4	1	Present	1 027	6 86	—	1 040	1 91	7 0	75
	9	Neg	1 024	5 83	0 4	1 040	—	6 7	42
	30	—	1 028	7 20	—	—	—	—	—
5	2	Present	1 028	7 20	—	1 041	1 49	7 3	68
	9	Neg	1 025	6 17	0 8	1 033	0 89	3 0	42
	13	Neg	—	—	—	—	—	2 8	—
	22	Neg	1 021	4 80	—	—	—	8 1	—
	38	—	1 026	—	—	—	—	—	—
6	2	Present	1 026	6 52	—	1 038	1 30	6 3	94
7	2	Present	1 026	6 52	—	1 038	1 36	6 6	78
8	2	Oxyhb	1 026	6 52	0 4	1 041	2 20	7 6	38
	32	—	1 029	7 55	—	—	—	—	—
9	1	Present	—	—	—	—	—	—	—
	15	Neg	1 028	7 20	0 4	1 047	2 36	9 1	56
	36	Neg	1 030	7 80	—	—	—	14 5	—
	42	—	1 029	7 55	—	—	—	—	—
10	0	Present	1 025	6 17	2 0	—	1 09	6 3	—
11	0	Present	—	—	—	—	2 25	—	—
12	1	Present	1 026	6 52	—	1 045	3 52	11 9	Died
	2	Present	1 029	7 55	16 0	1 038	0 92	5 0	90
13	4	Present	1 035	9 60	—	1 045	1 08	4 9	Died 140
									Died
14	1	Present	—	—	—	—	0 34	—	54
	8	—	—	—	—	—	1 04	—	—
15	7	Present	—	—	—	—	2 82	—	60
16	0	Present	1 027	6 86	16 0	—	—	—	64
	2	Neg	1 026	6 52	1 6	—	—	—	38
	14	Neg	1 026	6 52	—	—	—	12 3	—
	23	Neg	1 028	7 20	—	—	—	14 5	—
	30	—	1 027	6 86	—	—	—	—	—
17	1	Present	1 024	5 83	10 0	—	1 76	8 1	56
	6	Neg	1 025	6 17	—	—	—	—	—
18	2	Present	—	—	1 0	—	2 50	7 7	—
	20	Neg	—	—	—	—	4 08	12 0	—

amount by haemolysis. The absorption band seen in the red was therefore taken to be that of methaemalbumin only. In comparison with methaemalbuminaemia, oxyhaemoglobinaemia, though constantly present in excess in the early stages, was not considered to be sufficiently diagnostic by itself of intravascular haemolysis, since it can be produced simply by the drawing of blood.

The red cell count made as soon after admission as possible varied between 340,000 and 3,520,000 per c mm. When a second count was made a further fall was found to have occurred in four cases, in one instance dropping in one

TABLE III

*Comparison of Haemoglobin Findings by Specific Gravity and Acid Haematin Methods*

Case	During haemolysis		After haemolysis	
	Specific gravity method	Hb gm per 100 c c acid haematin (Sahlb)	Specific gravity method	Hb gm per 100 c c acid haematin (Sahlb)
2	4.9	5.6	—	—
4	6.2	7.0	7.2	6.7
5	6.3	7.3	3.7	3.9
12	9.0	11.9	4.7	5.0

day from 3,520,000 to 920,000 per c mm. In relation to the red cell count the haemoglobin readings, made by the acid haematin method, were high initially because the extracorporeal haemoglobin was included. To determine the true haemoglobin use was made of the formula given by Phillips, Van Slyke, Dole, Emerson, Hamilton, and Archibald (1943). The formula is  $\text{haemoglobin gm per 100 c c} = 33.9 \times \frac{Gb - Gp}{1.097 - Gp}$  where  $Gb$  is the specific gravity of the blood and  $Gp$  that of the plasma. Illustrative examples are given in Table III.

It will be seen from the table that during haemolysis the haemoglobin results by the specific gravity formula were lower than those obtained by the acid haematin method, but that, when haemolysis had ceased, the readings by both methods corresponded closely to one another.

The blood-urea varied between 38 and 94 mg per 100 c c on admission. In five cases when a second estimation was made the blood-urea had fallen in all but one.

Although the plasma was usually dirty brown in colour, quantitative van den Bergh estimations were possible, though not with the same degree of accuracy as with clear plasma. The highest figure recorded was 16 units.

The method used for estimating the specific gravity of blood and plasma was the copper sulphate method described by Phillips, Van Slyke, Dole, Emerson, Hamilton, and Archibald (1943). To determine the plasma proteins they used Moore and Van Slyke's (1930) formula,  $\text{protein gm per 100 c c} = 343 (Gp - 1.007)$ , where  $Gp$  is the specific gravity of the plasma. The accuracy of this formula has been substantiated by Weech, Reeves, and

TABLE II  
Results of Blood Examinations

Case	Interval, days after onset	Plasma				Blood			
		Methaem- albumin	Specific gravity	Protein gm per 100 c c	van den Bergh units	Specific gravity	R B C millions per c mm	Hb gm per 100 c c (Sahli)	Urea mg per 100 c c
1	4	Present	1 024	5 83	—	1 044	1 91	8 0	40
	16	Neg	1 025	6 17	—	1 049	4 00	11 3	—
	27	Neg	1 028	7 20	—	—	—	14 5	—
	34	—	1 026	6 52	—	—	—	—	—
2	1	Present	1 029	7 55	—	1 043	2 39	7 7	60
	12	Present	1 035	9 60	—	1 043	1 35	5 6	—
	17	Neg	1 025	6 17	2 0	—	—	4 5	140
	38	—	1 026	6 52	—	—	—	—	—
3	0	Present	1 027	6 86	—	1 045	2 61	7 7	60
	10	Neg	1 025	6 17	0 4	—	—	—	36
	39	—	1 024	7 20	—	—	—	—	—
4	1	Present	1 027	6 86	—	1 040	1 91	7 0	75
	9	Neg	1 024	5 83	0 1	1 040	—	6 7	42
	30	—	1 028	7 20	—	—	—	—	—
5	2	Present	1 028	7 20	—	1 041	1 49	7 3	68
	9	Neg	1 025	6 17	0 8	1 033	0 89	3 9	42
	13	Neg	—	—	—	—	—	2 8	—
	22	Neg	1 021	4 80	—	—	—	8 1	—
	38	—	1 026	—	—	—	—	—	—
6	2	Present	1 026	6 52	—	1 038	1 30	6 3	94
7	2	Present	1 026	6 52	—	1 038	1 36	6 6	78
8	2	Oxyhb	1 026	6 52	0 4	1 041	2 20	7 6	38
	32	—	1 029	7 55	—	—	—	—	—
9	1	Present	—	—	—	—	—	—	—
	15	Neg	1 028	7 20	0 4	1 047	2 36	9 1	56
	36	Neg	1 030	7 89	—	—	—	14 5	—
	42	—	1 029	7 55	—	—	—	—	—
10	0	Present	1 025	6 17	2 0	—	1 09	6 3	—
11	0	Present	—	—	—	—	2 25	—	Died
12	1	Present	1 026	6 52	—	1 045	3 52	11 9	—
	2	Present	1 029	7 55	16 0	1 038	0 92	5 0	90
13	4	Present	1 035	9 60	—	1 045	1 08	4 9	Died
									140
14	1	Present	—	—	—	—	0 34	—	54
	8	—	—	—	—	—	1 64	—	—
15	7	Present	—	—	—	—	2 82	—	60
16	0	Present	1 027	6 86	16 0	—	—	—	64
	2	Neg	1 026	6 52	1 6	—	—	—	38
	14	Neg	1 026	6 52	—	—	—	12 3	—
	23	Neg	1 028	7 20	—	—	—	14 5	—
	30	—	1 027	6 86	—	—	—	—	—
17	1	Present	1 024	5 83	10 0	—	1 76	8 1	56
	6	Neg	1 025	6 17	—	—	—	—	—
18	2	Present	—	—	1 0	—	2 50	7 7	—
	20	Neg	—	—	—	—	4 08	12 0	—

plasma would account for the initial high plasma specific gravity, and its rapid removal from the blood-stream would explain the low blood specific gravity. Nitrogen retention accounts only to a small extent for a high specific gravity, since even in severe nephritis the maximum increase amounts to 0.0017 (Moore and Van Slyke, 1930). Fluid loss can also raise the plasma and blood specific gravity, and its presence in our series appeared certain on clinical grounds. This would have been confirmed if the blood specific gravity had been high, but the excessive loss of oxyhaemoglobin from the blood-stream more than offset the haemoconcentration which undoubtedly occurred. Study of the subsequent behaviour of the plasma specific gravities in seven cases showed that seven to 22 days after the onset of haemoglobinuria the range was low, 1.021 to 1.028 with an average of 1.025, and that 23 to 39 days after the onset it was normal, 1.026 to 1.030. The fall in the plasma specific gravity was due not only to the removal of oxyhaemoglobin from the plasma, but also to the removal by the liver of methaemalbumin formed from the plasma albumin. Another reason was probably restoration of blood-volume, but the specific gravity and haemoglobin figures by themselves were insufficient to prove this. The return to normal of the plasma specific gravity was quicker when only one haemolysis was probable than when several were likely, but the delay in recovery showed that the protein loss had been replaced slowly. It was suggested by Kopp (1942) that liver damage is the cause of the fall of plasma-proteins which he found to occur in therapeutic malaria, the return to normal taking two to three weeks. It is considered probable by analogy that in haemolysis in our series the deposition of haemosiderin, increasing with repeated haemolysis, caused temporary liver damage which interfered with protein synthesis.

### *Experimental Work*

The aetiological relationship between pamaquin haemoglobinuria and classical blackwater fever has for long been confusing. An attempt was made to elucidate the part played by pamaquin by repeating a course in two of the seven cases of haemoglobinuria which occurred in Ranchi in 1943. Haemoglobinuria did not recur, but it was thought that had a spectroscope been available evidence of haemolysis in the blood might have been detected. In mild cases of haemoglobinaemia, methaemalbumin may not be seen by direct spectroscopy. Fairley (1941) showed that even in such cases, by the addition of fresh concentrated ammonium sulphide to the plasma, the  $\alpha$  band of ammonium haemochromogen could be seen sharply defined at  $558\text{ }\mu\mu$ . This test, known as Schumm's test, was shown by Fairley to be specific for methaemalbumin, originally thought to be free haematin. It occurred to us that this test might prove to be a delicate one for intravascular haemolysis and accordingly a spectroscope was procured. After the present outbreak of haemoglobinuria occurred, it was decided to repeat 'blanket treatment', using Schumm's test on the plasma along with van den Bergh and urobilinogen estimations to detect the presence of haemolysis.



Goetsch (1936) Since a slight error in specific gravity leads to very misleading results, extreme accuracy of the copper sulphate solutions is necessary. The specific gravities of the solutions made up were confirmed by Capt W Somerville, I A O C, at the Ordnance Laboratories, Calcutta. The plasma-proteins of two of the cases of our series were estimated by a sulphuric acid digestion-colorimetric method and the results were almost identical with those predicted from the specific gravities.

The normal range of plasma-proteins is given by Wright (1940) as 6.5 to 8.5 gm per 100 c.c. Best and Taylor (1943) give the normal range of blood

TABLE IV

*Normal Specific Gravities and Plasma Proteins in Indian Troops*

Number of cases	Blood specific gravity	Number of cases	Plasma specific gravity	Protein equivalent gm per 100 c.c.
1	1.053	1	1.026	6.52
1	1.054	5	1.0265	6.69
2	1.055	3	1.027	6.86
2	1.057	7	1.028	7.20
3	1.058	3	1.0285	7.38
2	1.059	1	1.029	7.55
1	1.061			
1	1.063			

specific gravity as 1.050 to 1.060, and the average plasma specific gravity as 1.027. Table IV shows the specific gravities of blood and plasma in 20 Indian soldiers, mostly Sikhs, taken at random from a combatant unit in which two cases of pamaquin haemoglobinuria had occurred. The unit had been on suppressive mepacrine for about one year. The figures are almost identical with those given for Europeans and Americans.

In blackwater fever Foy and Kondi (1938) found the serum-proteins to range between 5.4 and 8.3 gm per 100 c.c., the average in 10 cases being 6.4 gm. The blood was taken at an unspecified time after the onset of haemoglobinuria. The blood and plasma specific gravities were estimated in the present series because it was thought that the liberation of blood pigments by haemolysis should raise the plasma specific gravity and protein. The results are recorded in Table II, and it will be seen that the initial readings of the plasma specific gravities, although estimated during or immediately after haemolysis, varied considerably. The range was from 1.024 to 1.035, corresponding to 5.83 to 9.60 gm of protein per 100 c.c. In two cases, with repeated haemolysis, the specific gravity had risen on the following day from 1.026 to 1.029, and from 1.029 to 1.035 respectively. Blood specific gravities recorded in 10 cases were low, the range being from 1.038 to 1.045.

From these figures, therefore, it can be inferred that the plasma specific gravity was high if estimated during haemolysis and low if haemolysis had ceased. During haemolysis oxyhaemoglobin liberated from the red cells into the plasma is rapidly removed from the blood-stream by the reticulo-endothelial system and kidneys. The presence of oxyhaemoglobin in the

6	28 44	31 8 44	b d	P 2 P 4 P 5 C 1 C 2 C 3 C 5 C 6	Neg Neg Neg + + + Neg Neg	— 0 4 — — 3 0 — — —	Normal — Normal Normal + + — —	After 0 1 gm , palpitations, weakness, dyspnoea, gid diness, and thirst	Urine darker at C 1 Slight jaundice at C 2 for 2 days Temp 100° at C 2 and C 3
7	28 44	31 8 44	b d	P 3 P 4 P 5 C 1 C 2 C 3 C 5 C 6	Neg + + + + Weak + Neg Neg	— 3 0 2 0 — 0 6 — — —	+ — ++ ++ ++ ++ — Normal	After 0 1 gm , epigastric pain, anorexia, weakness, headcho, palpitations, and thirst	Urine darker at P 3 Slight jaundice from P 5 for 3 days Temp 98 8° at P 4
8	08 44	31 8 44	b d.	P 3 P 5 C 1 C 2 C 3 C 6	Neg Neg Weak + Neg Neg	— — — — — —	— Normal + Normal Normal	Dyspnoea on slight ex- ertion	Nil
9	27 7 44	28 8 44	b d	P 4 P 5 C 1 C 2 C 4 C 5	+ + + + + Neg	— 8 0 0 0 4 0 0 4 0 4	— ++ + ++ Normal Normal	After 0 1 gm , giddiness, weakness, epigastric burn, ing sensation, anorexia, and palpitations	Urine darker at P 4 Slight jaundice from P 5 for 5 days
10	20 8 44	13 0 44 (Pamaquin only)	b d	P 1 P 4 P 5 C 1 C 2 C 3	Neg Neg Neg Neg Neg Neg	0 4 — 0 4 0 4 — —	Nil Normal Normal + Normal Normal	Nil	Nil
16	20 7 44	28 8 44	b d	P 4 P 5 C 1 C 2 C 4 C 6	Neg + + + + Neg	— 4 0 2 0 0 8 0 4 —	— ++ Normal ++ Normal Normal	Nil	Urine darker with slight jaundice at P 5 lasting 3 days
17	28 44	13 0 44 (Pamaquin only)	b.d	P 1 P 4 P 5 C 1 C 2 C 3 C 4	Neg Neg Neg + + Neg Neg	— 2 5 4 0 — 0 4 —	Normal Normal + ++ Normal Normal	Nil	Slight jaundice at P 5 lasting 4 days

## Results of Test 'Blanket Treatment'

(Mopacrine 5 days, rest 2 days, pamaquin 5 days)

Case	Date of onset of haemo- globinuria	Date of test 'blanket treatment'	Day of treatment			Schumm's test for methaem- albumin	van den Bergh units	Urobil- inogen	Symptoms	Signs
			Pamaquin 0.01 gm	R = Rest	C = After pamaquin M = Mopacrine					
1	5 8 44	28 8 44	b d			+	—	—	After 0.1 gm. anorexia, epigastric pain, giddiness, palpitations	Urine darker
						+	10	+		
						+	0.4	Normal		
						+	0.4	++		
2	30 7 44	31 8 44	t d s			Neg	—	—	After 0.09 gm. headache, backache, and giddiness	Urine darker at P 2 Slight jaundice and temp 99.8° at P 4
						Weak +	20	+		
						+	20	Normal		
						+	30	++		
						+	30	++		
						Weak +	15	++		
						Neg	0.4	++		
						Neg	0.4	+		
								Normal		
3	31 7 44	31 8 44	t d s			Neg	—	—	After 0.12 gm. headache, backache, and epigastric pain	Urine darker at P 2 Slight jaundice at P 5 for 3 days. Temp 99.8° at P 5
						Neg	20	+		
						Neg	20	Normal		
						+	30	++		
						+	0.8	+		
						Neg	—	Normal		
						Weak +	20	+		
						+	20	+		
						+	40	++		
4	1 8 44	31 8 44	t d s			+	0.8	++	After 0.11 gm. epigastric pain, headache, chill, nau- sea, and vomiting Pama- quin had to be stopped at P 4.	Urine darker at P 2 Slight jaundice for 5 days from P 4 Temp 99.8° at P 4
						+	0.4	Normal		
						Neg	—	Normal		
						Neg	—	Normal		
						Weak +	20	+		
						+	20	+		
						+	40	++		
						+	0.8	++		
						+	0.4	Normal		
5	2 8 44	8 9 44	b d			Neg	—	Normal	After 0.09 gm. headache and anorexia	Temp 99.2° at C 1
						Neg	—	Normal		
						Neg	—	Normal		
						Neg	0.4	Normal		
						Neg	0.6	Normal		
						Neg	—	Normal		
						Neg	0.4	Normal		
						Neg	0.8	Normal		
						Neg	0.8	Normal		
						Neg	0.8	Normal		
						Neg	0.6	Normal		
						Neg	—	Normal		

had ceased. The results are given in Table V. For the sake of clarity the results of direct spectroscopy for methaemalbuminaemia, intracorpuseular methaemoglobin, and haemoglobinuria have been omitted from the table. They were in all cases negative. Two of the 11 cases of pamaquin haemoglobinuria (Cases 5 and 8) and the one case of doubtful aetiology (Case 10) showed no evidence of intravascular haemolysis. The nine remaining cases

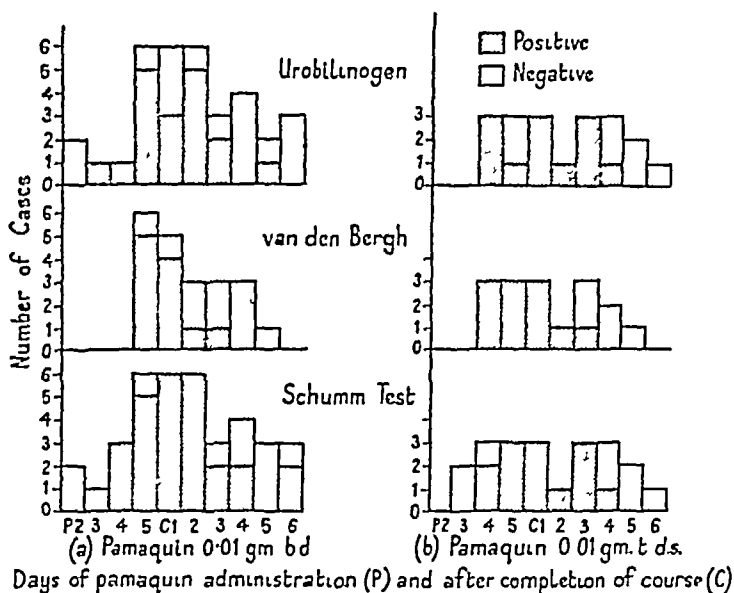
TABLE VI

*Effects of Combined Mepacrine and Pamaquin*

Case	Stage of treatment	Oxy-Hb	Schumm test	van den Bergh, units per 100 c c	Urobilinogen	Symptoms	Signs
5	M4 P4	Trace	Neg	0.4	Normal	After 3 days, backache, giddiness, weakness, thirst Temp 98.8° F, urine lasted until C2	Dark brown urine
	M4 P5	Trace	Neg	—	+		
	C1	Trace	+	1.0	—		
	C2	+	+	—	—		
	C4	+	Neg	0.4	Normal		
8	M3 P3	+	Neg	—	+	After 1 day, backache, giddiness, thirst, weakness, splenic pain, no fever. Became worse and 1 day's rest was given. Symptoms then recurred and disappeared completely on C3	Dark brown urine
	M4 P4	+	Weak+	—	++		
	M5 P5	+	+	—	—		
	C1	++	+	0.6	Normal		
	C3	Trace	Neg	0.8	Normal		
	C5	Trace	Neg	—	Normal		
10	M4 P4	Trace	Neg	0.4	Normal	After 2 days, backache, giddiness, weakness, no fever. Lasted till C2	Dark urine
	M5 P5	Trace	+	0.8	+		
	C1	Trace	+	0.8	—		
	C2	Trace	+	1.5	++		
	C4	Trace	+	0.4	+		
	C6	Trace	+	—	Normal		

all showed positive Schumm tests and increased blood-bilirubin and urobilinogen in the urine. The symptoms complained of by these patients were epigastric pain, headache, anorexia, thirst, giddiness, weakness, dyspnoea on slight exertion, backache, and palpitations, and in one case nausea and vomiting. Two patients were free from symptoms. The signs were early darkening of the urine in all cases, slight jaundice corresponding to van den Bergh readings of 2 to 8 units (eight cases), and slight fever varying between 98.8° and 100° F (five cases). Blood slides showed no malarial parasites. The jaundice lasted three to five days. The symptoms bore a direct relationship to the dosage of pamaquin. They began as a rule after 0.09 to 0.12 gm, that is, after three or four days of pamaquin when given thrice daily, in three cases, or five days when given twice daily, in six cases. The correlation between increased urobilinogen, blood-bilirubin, and methaemalbuminaemia is shown in the figure. It will be seen that Schumm's test remained positive about one day after the van den Bergh test had returned to normal. This is not surprising since methaemalbumin is formed from extracorpuseular haemoglobin liberated by haemolysis, and is only slowly removed from the blood-stream.

**Method** The reagent used was fresh concentrated ammonium sulphide, but concentrated ammonium polysulphide (yellow ammonium sulphide) was tried later and gave the same results. The addition of a few drops of ammonia, as described by Fairley, was not found to be necessary with the brand of reagent used. These chemicals were obtained through the courtesy of Dr John Lowe from the Calcutta School of Tropical Medicine. One-tenth c c of reagent is



Correlation between increased urobilinogen, hyperbilirubinaemia, and methaemalbuminaemia with experimental pamaquin

Note Only van den Bergh readings of 1 unit and over have been recorded as positive in this figure

added under ether to 10 c c of plasma and the mixture shaken. The reading is made in five to ten minutes, since in weakly positive cases the  $\alpha$  band of haemochromogen is slow in appearing. If oxyhaemoglobin is present in excess, the band of reduced haemoglobin produced obscures the  $\alpha$  band of haemochromogen. The trace of oxyhaemoglobin often present as the result of drawing blood is insufficient to interfere with the test. A false positive is obtained if excessive reagent or alkali is present. Therefore the reagent used should be tested for excessive alkalinity to see if haemochromogen is produced with normal blood which has been laked.

A test pamaquin course of 0.02 gm daily for five days was given to the two early cases (Cases 14 and 15), and neither haemoglobinuria nor methaemalbuminaemia by direct spectroscopy was detected. Schumm's test was not used nor a complete investigation made. In 12 of the subsequent cases further 'blanket treatment', including pamaquin for five days, was carried out, with two exceptions (Cases 10 and 17) where only a pamaquin course was given. These tests were made approximately one month after haemolysis

0.01 gm twice daily for five days, and in three Schumm's test became positive the day after completion of the course, but no other sign or symptom of haemolysis was evident. As shown in Table V, two of the haemoglobinuria patients were given a similar test course of pamaquin and in one of them well-marked haemolysis with jaundice occurred. It must be re-emphasized that all the tests recorded in the present paper were carried out on Indian troops only.

*'Formes Frustes' of Blackwater Fever*

In classical blackwater fever *formes frustes* can occur. For example, de Langen and Lichtenstein (1936) described such cases with mild attacks of fever, with or without jaundice, with pale pink urine. It would be surprising if similar cases did not occur with intravascular haemolysis due to pamaquin. The experience of one unit which received 'blanket treatment' is therefore of interest. This unit, an Indian Mobile Workshop consisting of 200 men, was so treated from the 27th to the 31st July 1944. Thirty-six men reported sick direct to our hospital with the following symptoms:

Jaundice, high coloured urine, epigastric pain, anorexia	9
High coloured urine, epigastric pain, anorexia	18
Epigastric pain, giddiness	3
Epigastric pain, diarrhoea	2
Mixed symptomatology	4

Two of the nine men who were jaundiced showed frank haemoglobinuria, and are Cases 1 and 2 of our series. The remaining seven were discharged from hospital after a few days when the jaundice had disappeared. It was not possible to obtain direct information from other units regarding their sick rate at the end of 'blanket treatment', as these units were not static. A larger number of cases than usual of infective hepatitis passed through our hospital at that time and some of these were possibly *formes frustes* of blackwater fever. An attempt was made over a period of two months to discover cases of transient haemoglobinuria by a daily examination and urine inspection of 3,000 patients during the pamaquin course. About 10 per cent complained of vague symptoms such as anorexia, giddiness, palpitations, and weakness, symptoms which hitherto had been attributed entirely to the effects of the malarial attack. Towards the end of the course in this group, discoloration of the conjunctivae and darkening in the colour of the urine was common. Jaundice was rare. These patients with jaundice were investigated and six cases of apparent *formes frustes* were discovered, of which one example may be given. A Hindu aged 20, Arakan service seven months, was admitted to hospital with malignant tertian malaria. On the fifth day of pamaquin he complained of nausea, vomiting, and lethargy, and stated that his urine was highly coloured. The next day slight jaundice was seen, and the urine was dark and contained increased urobilinogen but no bile pigment. Direct spectroscopy of the urine showed neither oxyhaemoglobin nor methaemoglobin, but on adding equal amounts of ammonia and concentrated ammonium sulphide, haemochromogen was seen, indicating the presence of

*Combined effect of mepacrine and pamaquin* It remained to be seen if the action of suppressive mepacrine had had any effect on the production of pamaquin haemoglobinuria. Mepacrine is a cumulative drug and had been taken, often for long periods, before 'blanket treatment' was given. The administration of pamaquin under these conditions was probably tantamount to giving both drugs simultaneously, a combination usually considered toxic. When test 'blanket treatment' was commenced, one month after the cessation of haemoglobinuria, most of the stored mepacrine had already been excreted, as shown by negative urines tested by an ether extraction-hydrochloric acid method. Therefore the conditions obtaining with routine 'blanket treatment', which followed directly on suppressive mepacrine, were not fully reproduced. In an attempt to elucidate the part played by suppressive mepacrine, mepacrine 0.1 gm t.d.s. and pamaquin 0.01 gm b.d. for five days were given simultaneously after a further two weeks to the three cases previously negative to experimental pamaquin. Intravascular haemolysis then occurred. The results are shown in Table VI.

*Intradermal Tests* A 0.1 per cent solution of pamaquin hydrochloride was made by dissolving pamaquin in its equivalent amount of hydrochloric acid. One-tenth c.c. of this solution was given intradermally to six patients who had had haemoglobinuria and to six normal subjects. Positive skin reactions occurred neither in the patients nor in the controls.

*In vitro experiments* Difficulty was experienced in conducting *in vitro* experiments because it was not possible to obtain pamaquin in powder form and it was thought that the excipient of a tablet might introduce complicating factors. However, a pamaquin tablet was used and a hydrochloride solution made up in the serum of the haemoglobinuric patient to be tested. Haemolysis of the red cells of three convalescent patients was inspected microscopically and was seen to occur in pamaquin dilutions of about 1/200 to 1/1,000. As these concentrations bore no relation to those *in vivo* this line of investigation was given up.

*Routine malaria treatment* Patients undergoing routine treatment for malaria were compared with those subjected to the 'blanket treatment' experiment. Thirty-one Indian patients were followed through from untreated malaria, mostly malignant tertian, to the end of the pamaquin course. Schumm's test was positive in 24 at the untreated stage, but seven whose Schumm tests became negative during the rest period became positive again towards the end of their course, although they showed no other evidence of intravascular haemolysis. There was no clinical or laboratory evidence of a recrudescence of malaria in these cases.

*Controls with pamaquin alone* Schumm's test was carried out on nine healthy Indian soldiers and 44 Indian patients in whom there was no clinical evidence of malaria. It was found to be positive in 10 of the patients, the methaemalbuminaemia being possibly due to the activity of chronic malaria. Six healthy patients, whose Schumm's tests had been negative and who had not previously received mepacrine, were given a test course of pamaquin.

plays an essential part in haemolysis, with quinine and other haemolytic agents as contributory or exciting factors. There are other subsidiary factors, for example chill and exertion, which can influence the haemolysis in blackwater fever. The factors which might have initiated or intensified the haemoglobinuria in our series will now be discussed.

*Lack of rest* Warnings regarding the dangers of pamaquin administration have been repeatedly given by the Army medical authorities, and 'excused duty during pamaquin and for 48 hours thereafter' was ordered in Medical Directorate of India Technical Instructions No. 12, dated December 14, 1943. Almost all our patients who received 'blanket treatment' were, however, carrying out their normal duties during its administration. In one case, a man marched 12 miles in one day in order to collect his unit's rations. Another drove over 60 miles in a truck along a very bad road. Two others levelled ground for basha construction. An additional adverse factor was a rough ambulance journey of up to 12 miles after haemoglobinuria had commenced. It is noteworthy that all the deaths occurred in the group on 'blanket treatment' and none in the routine treatment group. Blacklock and MacDonald (1928) believed that blackwater fever may be explained by a local increase of lactic acid in the spleen, which they showed was haemolytic *in vitro* and *in vivo*. This theory was discredited by Ross (1932) as lacking adequate experimental justification. He showed that, *in vitro*, haemolysis was not due specifically to the lactic acid, but to the lowering of pH to 5.2. He also pointed out that there was no increase in lactic acid in the peripheral blood in blackwater fever nor in malignant tertian malaria patients who had previously suffered from blackwater fever. Ross admitted that it was not feasible to estimate blood lactic acid just prior to the onset of blackwater fever, and this is one objection to his criticism. It is known that haemoglobinuria may occur after severe exercise, when blood lactic acid may be increased from 20 to over 400 mg per 100 c.c. Gilligan, Altschule, and Katersky (1943) found haemoglobinuria in four and haemoglobinaemia in 18 of 22 athletes who finished the 26.2 miles marathon race. Thus though Blacklock and MacDonald's lactic acid theory was based on insufficient experimental evidence it has not been entirely disproved. By whatever mechanism exercise precipitates or aggravates haemolysis it is certainly a factor of importance. It is therefore probable that exercise did play a part in the haemoglobinuria of the group on 'blanket treatment', but that it was only a minor factor was shown by the occurrence of haemoglobinuria in patients while at rest in hospital.

*Dosage* Because it was recognized that Indian troops were more prone than British to the toxic effects of pamaquin, the daily dose prescribed for their routine treatment in the army was reduced to 0.02 gm. In 'blanket treatment', however, 0.03 gm was prescribed irrespective of nationality and this dose was given in all our cases, symptoms occurring usually on the second or third day of pamaquin. When test 'blanket treatment' was applied subsequently the cases given 0.02 gm of pamaquin daily developed



blood pigment The plasma showed no methaemalbumin, but Schumm's test was positive No intracorpuseular methaemoglobin was seen The following day the van den Bergh reading was 10 units, and urobilinogen was still much increased, but no blood pigment was present in the urine The bilirubin returned to normal in two days Schumm's test became negative one week after completion of the pamaquin course Anaemia was not a feature of this case. In another case test 'blanket treatment' was subsequently given Schumm's test became positive on the fifth day of pamaquin, and remained positive for four days There was an increase in blood-bilirubin and in urobilinogen. It was regrettable that conditions made it impossible to investigate the rest of the cases showing symptoms other than jaundice at the end of their pamaquin course Our hospital, the most forward in the Arakan theatre of war, admitted some 50,000 cases in the year, of which nearly one-half were detained for clinical and laboratory investigation and treatment, and were returned to their units The heavy routine work involved precluded a more thorough search for other cases of *formes frustes*, several of which must have been missed There is little doubt that the incidence during routine malarial treatment was much more than the six cases (0.2 per cent) appear to have indicated We realize that there are many shortcomings in the present investigation which otherwise would have proved more satisfactory and the results more conclusive The medical staff was sadly depleted for many months and a more detailed investigation and follow-up of our cases was therefore unfortunately impossible

### Discussion

Experiments *in vitro* (Torrioli, 1929, Dikshit, 1936, Chopra, 1936) have shown that pamaquin is a haemolytic drug, but that the concentration required to produce haemolysis is very much higher than that obtained *in vivo* by therapeutic dosage This is also true of quinine, which, because of its association with blackwater fever, has received much more attention Fairley and Murgatroyd (1940) suggested that quinine is haemolytic *in vivo* when malaria is active Mer, Birnbaum, and Khgler (1940) showed that, using ox bile as a haemolytic agent, the erythrocytes of malarial subjects were haemolysed more readily when quinine with or without pamaquin had been given previously Fairley (1940) suggested that the greater tendency to haemolysis in chronic malaria is due to hypertrophy of the reticulo-endothelial system Foy and Kondi (1943), however, considered that the evidence for the part played by the reticulo-endothelial system in haemolysis is insufficient, and that hypertrophy of this system cannot explain a sudden haemoclastic crisis These authors postulated instead an increase of lysolecithin formed from stagnant blood in an enlarged spleen An entirely different concept of haemolysis was put forward by Maegraith, Findlay, and Martin (1943) Their view is that a haemolytic enzyme normally exists which is inhibited by a substance reduced in amount in blackwater fever and acute malaria These theories are based on the premise that malaria

Mepacrine had been given in all our cases, both those on 'blanket treatment' and those not so treated, and is therefore suspect as a factor contributing to the haemolysis with pamaquin. The reason for mepacrine enhancing the toxic effects of pamaquin is not known.

*Malaria* Most of our haemoglobinuria patients denied having had malaria before admission. This was in contrast to the histories given by ordinary malaria patients, half of whom described one or more previous attacks in the year. Blood-films of the group on 'blanket treatment' on admission were positive in three (malignant tertian) and negative in nine cases, and the spleen was enlarged in half of the cases of this group. The presence of splenomegaly in some of these cases suggested that chronic malaria existed, damped down by suppressive mepacrine. Apart from these cases the remainder did not appear to have been suffering from malaria. Moreover, in the group not given 'blanket treatment' the attack had been adequately treated by the time pamaquin was given, and neither acute malaria, quinine, nor mepacrine had produced haemoglobinuria. Hyperbilirubinaemia, increased urobilinogen, and a continued positive Schumm test, in the absence of severe anaemia, may be taken as presumptive evidence for the activity of chronic malaria. Thus in apparently non-malarial Indian patients in our hospital 20 per cent had a positive Schumm's test, and in tea-garden coolies with splenic enlargement 50 per cent had van den Bergh readings of one unit and over (Napier and Das Gupta, 1937). In our series, however, Schumm's test became negative again soon after test 'blanket treatment', and blood-bilirubin and urinary urobilinogen returned to normal. Although a negative Schumm's test does not necessarily exclude the presence of chronic malaria it may be taken to indicate that the disease is quiescent.

Thus although malaria was a factor in some cases, there is insufficient reason for believing that it played an important role in them all.

*Blackwater fever* It is generally considered that in blackwater fever there is a predisposing cause, chronic malaria, which produces an increased tendency of red cells to haemolysis. The principal exciting causes are said to be fresh attacks of malaria and the administration of antimalarial drugs. The possibility must therefore be considered that in our series conditions were ripe for haemolysis before pamaquin was given. However, as has already been shown, the evidence for the activity of both acute and chronic malaria as aetiological factors in our series was weak. Moreover, blackwater fever precipitated by malaria or quinine is extremely rare in the Arakan. Furthermore, the condition could be reproduced in a modified form by the administration of experimental pamaquin. There is no reason to suppose therefore that our patients were suffering from classical blackwater fever.

*Liver damage* Chopra (1936) stated that pamaquin exerts an indirect haemolytic effect by impairing the detoxicating function of the liver, and Ghosh (1944) that the symptoms of pamaquin poisoning appear in those whose liver is already damaged. In the present series as any liver damage

signs and symptoms of intravascular haemolysis one or two days later than those who received 0.03 gm daily. Moreover, malaria patients on 0.02 gm daily did not develop haemoglobinuria till the end of their course. It is considered likely that, had the dose in 'blanket treatment' consisted of 0.02 gm pamaquin daily, haemoglobinuria would have occurred one or two days later than it did and that simple overdosage of the degree actually given was not an important aetiological factor.

*Batch toxicity* This was *a priori* most unlikely since cases were relatively so few and the units in which they occurred so scattered. Nevertheless, the complete stock of pamaquin remaining after 'blanket treatment' in XV Infantry Corps was taken over and used solely in our malaria annexe. As a control, our own stock continued to be used for patients, approximately equal in number, in other malaria wards. No case of haemoglobinuria occurred in a total of 3,000 patients treated in two months and *formes frustes* were no more frequent in the malaria annexe than in the other malaria wards.

There is therefore no evidence that batch toxicity existed.

*Race* All our cases occurred in Indian troops, mostly Punjabis. How much significance should be attached to this fact was difficult to determine, although the ratio of Punjabis to other Indians who received 'blanket treatment' was one to three. Although no case of haemoglobinuria in British troops was treated in our hospital, it must be pointed out that Indian troops far outnumbered British in this area. Amy (1934, 1935) also remarked on the fact that no British soldier developed pamaquin haemoglobinuria during the period in which he recorded 11 cases in Indians. It is known, however, that occasional cases do occur among British troops. It is apparent that some racial distinction does exist which may be connected with some such factor as chronic malaria which is more frequent in Indians.

*Suppressive mepacrine* Three cases of blackwater fever occurring after mepacrine given for malaria were described by Foy and Kondi (1937). The dosage in the two patients who survived was 0.1 gm t.d.s. for five days. One developed haemoglobinuria immediately on completion of this course and the other two days later. Blood films and spleen puncture were negative for malarial parasites 12 to 24 hours before the onset of haemoglobinuria. These authors conclude that in these cases malaria was not important in the genesis of the condition. Manson-Bahr (1940) mentioned similar cases after mepacrine. Haemoglobinuria occurring after the combined use of mepacrine and plasmoquine is referred to by Strong (1942) and others.

The combination of mepacrine and pamaquin in treatment is condemned by most authorities and, as has already been pointed out, giving pamaquin to a patient with a considerable store of mepacrine in his tissues is equivalent to giving both drugs together. This was confirmed by giving both drugs simultaneously to the three patients who had been negative to experimental pamaquin, and they all became *formes frustes* of pamaquin haemoglobinuria.

who received it during routine treatment for malaria. Three deaths occurred in the group given 'blanket treatment'

2 Clinical and post-mortem findings were identical with those described in classical blackwater fever

3 Laboratory investigations included spectroscopy and plasma-protein estimation by a specific gravity method. Methaemalbumin was shown to be present in the plasma during the period of haemoglobinuria. Intracorpuseular methaemoglobin was seen neither in the cases described nor in 50 malaria cases on pamaquin. After an initial rise plasma specific gravity fell and gradually returned to normal. The delay suggests that there had been interference with protein synthesis

4 The differential diagnosis between classical blackwater fever and pamaquin haemoglobinuria is discussed. The presence or absence of cyanosis and intracorpuseular methaemoglobin is shown to be of no diagnostic importance

5 Treatment was by absolute rest, fluids, and alkalis, but in five cases antivenene was given intravenously

6 'Blanket treatment' or pamaquin alone was repeated in 12 cases. Intravascular haemolysis occurred in all except three, as shown by hyperbilirubinaemia, increased urobilinogen, and the presence of methaemalbuminaemia as shown by Schumm's test. In the three negative cases mepacrine and pamaquin given simultaneously produced intravascular haemolysis. Malarial and non-malarial patients are used as controls

7 Intradermal tests for pamaquin sensitivity were negative

8 *Formes frustes* of pamaquin haemoglobinuria are described

9 Aetiological factors discussed include lack of rest, dosage, batch toxicity, race, suppressive mepacrine, malaria, blackwater fever, liver damage, and toxicity of pamaquin

### *Conclusion*

The term blackwater fever describes a syndrome which has several causes. Definition on an aetiological basis is desirable. Thus haemoglobinuria due to malaria, quinine, mepacrine, or pamaquin, are terms which are preferable, being more accurate, though there may be common underlying factors present in varying degrees

As far as pamaquin haemoglobinuria in the present series is concerned, malaria appears to play a lesser role than it does in classical blackwater fever (malarial haemoglobinuria). Over-susceptibility to pamaquin is held to be the determining factor in producing the haemoglobinuria, with the previous administration of mepacrine an important contributory cause

Our thanks are due to those medical officers, especially Captains D Macaulay and R. N. Mitra, I A M C, who co-operated in this investigation in spite of being constantly overworked in the wards, to the Directors of the Calcutta School of Tropical Medicine, of The All-India Institute of Hygiene, Calcutta, and of the King Institute, Guindy, for their ready permission to use their libraries, to Brigadier I. G. W. Hill, Consulting Physician to

detected was probably due to the attack of haemoglobinuria itself, no inference of previous damage can be made. Indeed the fact that the plasma-proteins returned to normal suggests that there could have been no serious liver inefficiency.

*Pamaquin toxicity.* Judging by the varying degrees of haemolysis which occurred with pamaquin it appears that the patients can be graded into four groups

A Those in whom there is no evidence of intravascular haemolysis

B Those who show only a positive Schumm's test, symptoms in this group are vague or absent

C Those who have haemolysis as shown by a positive Schumm's test, hyperbilirubinaemia, and increase in urobilinogen, but no frank haemoglobinuria. This group constitutes *formes frustes* of haemoglobinuria and the signs and symptoms are jaundice, dark urine, anorexia, epigastric pain, vomiting, slight fever, weakness, giddiness, dyspnoea, palpitations, and thirst

D Those in which frank haemoglobinuria occurs. The signs and symptoms are identical with those of classical blackwater fever.

When test 'blanket treatment' was given, lack of rest, the cumulative effect of suppressive mepacrine, and acute malaria had been eliminated and therefore *formes frustes* occurred in cases which previously had developed haemoglobinuria. The effect of mepacrine had not been altogether eliminated as this drug had preceded pamaquin in almost all cases, and probably influenced the haemolysis which subsequently occurred. In normal subjects haemolysis as shown by Schumm's test occurred with pamaquin alone in three out of six cases. It is therefore evident that pamaquin by itself can be haemolytic *in vivo*. The question still remains to be answered why haemoglobinuria did not occur until pamaquin had been given, and the most likely answer seems to be that haemolysis was due to the toxicity of pamaquin. Chopra (1936) stated that gross overdosage with pamaquin produces haemoglobinuria, and that the lethal and therapeutic doses are not widely separated. This is the reason for the relatively high incidence of toxic manifestations.

Over-susceptibility to a drug is said to exist when symptoms of gross overdosage occur with therapeutic doses. In the present series a few tablets of pamaquin were sufficient to cause haemoglobinuria and its sub-clinical states, but the severity depended on dosage, exercise, suppressive mepacrine, and the activity of malaria. Haemolysis by pamaquin could be repeated experimentally. The view is therefore taken that an essential cause in producing the haemolysis was the toxicity of pamaquin in patients who were over-susceptible to the drug.

### Summary

1 Haemoglobinuria occurred in 13 out of 10,000 Indian troops who received pamaquin during 'blanket treatment' and in five out of 8,000 patients

# TEMPORAL ARTERITIS A GENERALIZED VASCULAR DISEASE<sup>1</sup>

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With Plates 1 to 5

## *Introduction*

OUR thesis is that there exists in elderly people a widespread arterial disease, not uncommon but rarely recognized, in which characteristic arterial and striking local signs occur, and in which inflammatory and degenerative changes in the walls of the affected arteries produce a characteristic histological picture. The syndrome we present appears identical with temporal arteritis, first described by Horton, Magath, and Brown in 1932. They reported two cases, the first, a woman of 58 years, suffered with severe headaches and inflamed and tender temporal arteries, the second, a man aged 68 years, complained of weakness, pain over the forehead, tender areas in the scalp, and had enlarged cervical glands and tender temporal arteries. Microscopical examination of excised portions of these arteries, consideration of the symptoms, and the apparently self-limiting course of the disease led them to postulate that the syndrome represented a new disease entity. Over the past 12 years at least 30 cases have been reported. The symptoms have been fairly uniform and occurring in patients over the age of 55 years. In some they have been suggestive of generalized arterial involvement, but until recently there has been no autopsy proof of this. Sproul (1942) reported briefly the pathological findings in one such case, whilst Gilmour (1941), under the title giant cell arteritis, has recorded three similar cases. Chasnoff and Vorzimer (1944) have also described the clinical details of a case which they stated showed diffuse arterial changes at autopsy.

We have had under observation seven patients with the disease between the ages of 66 and 73 years, three male and four female (Table 1). The onset of the illness in six of the cases was with general malaise, myalgia and arthralgia, anorexia, and loss of weight. After some months, nine in one case, more striking symptoms appeared. Headache was severe at some time in all the cases. Mental confusion was present in two cases for a period. In six cases, and probably in the seventh, the temporal arteries showed thrombosis. Three patients suffered complete loss of sight, one loss of sight in one

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Fourteenth Army, for his sympathetic interest, and to Lieutenant-Colonel W I Card, R A M C, for some corrections in the manuscript, to Colonel J W Eames, Officer Commanding the hospital, and to Major-General T. O Thompson, Director of Medical Services 11th Army Group for permission to publish

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eye, and two slight visual impairment, in only one were there no visual symptoms. Six had symptoms suggesting generalized arterial disease, confirmed by autopsy in two cases. Raised protein in the cerebrospinal fluid was found in three cases, without associated pleocytosis. Moderate hypochromic anaemia was present in four cases. A variable degree of pyrexia was present in four cases, in one as high as 103° F. The histopathological features were consistent with a common pathological process. The full case histories are given in the Appendix.

### *Clinical Features*

*Age and sex incidence* Up to and including the present series, 37 cases have been reported under the diagnosis of temporal arteritis. All have been over the age of 55 years and the oldest was 80 years (Johnson, 1943). Twenty-five were in women, and 12 in men.

*Constitutional symptoms* Though temporal artery thrombosis has been the common diagnostic feature of all the reported cases, consideration of these reveals that systemic manifestations have been previously present. Generalized muscle aches and soreness, painful knees, shoulders and hips, fever and night sweats, lassitude, weakness, anorexia, and marked loss of weight have all been reported to occur over periods up to nine months before the appearance of any more dramatic symptoms such as temporal artery thrombosis or visual disturbance. In only one of our patients did these symptoms appear to be of minor importance. Joint swellings, sore muscles, and stiff joints have been reported by a number of writers. In our Case 2 there was extreme tenderness of muscles. Case 3 had 'rheumatoid' changes in her wrists and prolonged vague muscle pains. Case 5 had had muscle pains and tenderness and joint swellings over the previous 12 months. Case 6 stopped work at the age of 72 years on account of her malaise, joint swellings, and general aches and pains six months before the occurrence of loss of vision. Including those reported cases in which few clinical features are given, approximately half, such generalized symptoms have been the first sign of illness.

*Headache* Headache is a constant feature. It usually begins as a generalized ache. Later, when the temporal arteries are affected, frontal or temporal headache becomes severe, and when the occipital arteries are involved, pain in the neck and up the back of the head is a prominent symptom. It has been described as a dull boring pain, a throbbing pain, and occasionally as a lancinating pain. It is usually severe and constant. Bowers (1940) described the headache as constant, dull, and throbbing, usually disturbing the patients' sleep at night, not associated with effort or posture, and so severe as to cause almost complete unwillingness to eat. Coughing and sneezing frequently aggravate the pain. In our Case 4 occipital headache was present for six weeks, preventing sleep or frequently waking him from such sleep as he had. When the temporal arteries became involved, in his case there was exacerbation of the headaches and a shift to the temporal region. Headaches of greatest severity are often associated with involvement of



TABLE I

	Temporal artery	Duration of illness	Systemic symptoms	Headache	Visual symptoms	Blood-pressure	Maximum temperature °F	Red cells, millions per c mm	Hæmoglobin	White cells per c mm	Cerebrospinal fluid
1 M 66	Biopsy positive	6 months Dead	Intermittent claudication, lack of energy, anorexia	++	Bliss 24 hrs Permanent loss of vision right eye	130/80	100	4.79	96	11,850	Protein 130 mg No increase in cells W R negative
2 F 66	No biopsy	10 months	Malaise, severe 'rheumatic' pains, polyuria, anorexia	++	Diplopia 3 days, complete loss of vision	130/75	99.6	3.62	70	10,700	Protein 70 mg No increase in cells W R negative
3 F 69	Biopsy positive Autopsy	30 months	Joint swellings, generalized muscle pains, thromboses in arms and legs	++	Diplopia, complete loss of vision	100/105	Normal	3.94	72	5,100	Not done
4 M 71	Biopsy positive	Over 30 months	Slight general malaise	+++	Nil	150/95	Normal	4.20	60	8,400	Protein 70 mg No increase in cells W R negative
5 M 69	Biopsy positive	Over 12 months	Joint pains and swellings, anorexia, lassitude, general malaise, loss of weight	+++	Transient blurring of vision Slight residual restriction of vision	180/90	99.4	4.85	98	10,500 (Eos 6.7%)	Protein 36 mg No increase in cells W R negative
6 F 73	Biopsy positive Autopsy	14 months	Joint swellings, loss of weight, lassitude, 'rheumatism'	++	Diplopia, complete loss of vision	145/70	Normal	3.90	74	8,350	Protein 47 mg No increase in cells W R negative
7 F 68	Biopsy positive	Over 12 months	Loss of weight, 'rheumatism'	+++	Slight deterioration	140/80	103.0	4.30	80	13,000	Protein 32 mg No increase in cells W R negative

*Ocular and oculomotor symptoms* Horton and Magath (1937) observed temporary diplopia in one of their eight cases. In two examination of the fundi showed evidence of 'phlebitis of one of the retinal veins' with haemorrhages and exudates. Jennings (1938) described visual symptoms which appeared nearly nine months after the onset of the illness. 'A spot appeared in front of the left eye and during the next five days, it was as though a curtain was being drawn over the left eye, removing all sight'. At the same time the patient complained of mistiness of vision and photophobia in the right eye. On examination the left eye was blind with a large inactive pupil, a pale disk, and a small central haemorrhage. There was pain on lateral movement of the eye. While at first no changes were noted in the right eye, pallor was noted later in the disk, and loss of the lower half of the visual field was also noted. Subsequently the vision in this eye improved, and the patient was able to read large print, though the visual field showed very little change. Bain (1938) described photophobia and 'peripapillary atrophy' in his case, but there was no upset in vision apparent. Dick and Freeman (1940) noted visual disturbance in both their cases, in Case 1, the vision in the left eye became blurred some weeks after the scalp arteries had become involved. The optic disk was noted to be twice the normal size. There was also a small haemorrhage in the left eye and the visual field was reduced to a small area. No further observations were made upon the subsequent course. In Case 2 soreness of the eyes and blurred vision followed shortly after involvement of both temporal arteries. Diplopia was present for a week. Sluggish extra-ocular movements and poor vision in the right eye were noted. No record, however, was made of the ophthalmoscopic appearances.

Careful observation on three cases was made by Johnson, Harley, and Horton (1943). Their first patient noticed diminution of vision lasting for four days in the right eye six months after the onset of her illness. She then noted inability to see in the lower half of the field of vision of the left eye, one week later the field in her right eye became reduced as though she were looking through a slit, and the vision in the left eye gradually disappeared entirely. On examination one week later 'vision was 6/6 in the right eye, and vision in the left eye reduced to perception of light. The field of the right eye revealed loss of the superior nasal quadrant and general constriction. In the ocular fundus several ischaemic regions were present along the superior temporal vessels. In the fundus of the left eye occlusion of the upper branches of the central retinal artery and vein with fragmentation of the bloodstream was noted. Ischaemic oedema of the disk, which was elevated two diopters at the upper part, was present. In both eyes the loss of vision appeared out of proportion to the ophthalmoscopic findings'. In this patient the vision in the left eye remained very poor, but that in the right improved with some widening of the field of vision. In their second case the discrepancy between the ophthalmoscopic findings and visual symptoms was even more marked. Both eyes suffered complete loss of vision with a week

a fresh artery At times they may be resistant to morphine and the usual analgesic drugs

*Cerebral symptoms* Many cerebral symptoms have been noted Case 2 was admitted to hospital as a case of cerebral tumour suffering from severe headache, vomiting, and papilloedema Case 3 was for eight weeks seriously disorientated, and at times delirious She made a fairly good recovery from this episode, but at autopsy 18 months later, sections of the brain showed old and recent multiple arterial thromboses Case 6 suffered from a number of attacks of vertigo whilst in hospital She then became deaf in the right ear, and shortly afterwards completely deaf At the same time she became mentally confused, incontinent of urine and faeces, and had to be restrained from getting out of bed She appeared to be in an irrecoverable state This episode lasted one week, and then over a period of five days her hearing returned, although she still was occasionally incontinent and querulous After a further two weeks she became drowsy and comatose, dying within 72 hours Severe cerebral nausea and vomiting were recorded by Johnson, Harley, and Horton (1943), and were also present in our Cases 2 and 6 Murphy (1942) described vertigo, exhaustion, and headache persisting for six months after the development of arteritis Chasnoff and Vorzimer (1944) ascribed the prolonged coma in their case to multiple cerebral thromboses Schaefer and Sanders (1942) reported a case in a 62-year old woman where 'The headache was unbearable and could not be controlled with 1/2 gr of morphine intramuscularly She appeared desperately ill, did not respond very well and her speech became slurred Finally, the patient became delirious and the possibility of brain tumour with increased intracranial pressure was considered Neurological examination was, however, negative except for doubtful Babinski and Chaddock reflexes on the left' Six weeks later the patient had made a remarkable recovery, being alert and free from symptoms Sprague and MacKenzie's (1940) patient also manifested a period of great mental sluggishness so that 'he was thought to have had a cerebro-vascular accident' He made a good recovery In the case reported by Bowers (1940) coma lasted for five days and vertigo was present for some time after recovery took place This episode followed six months after temporal artery involvement Bowers considered that, though the patient had hypertension, the cerebral arteries might have been involved by a similar process to that in temporal arteritis Temporo-mandibular pain was present in 11 of the reported cases, and in two of our cases It was severe enough in one case (Dick and Freeman, 1940, Case 1) to make the patient fear eating or opening her mouth Difficulty in chewing food was present in the majority of cases Occasionally, actual swelling was present in the temporo-mandibular joint (Hoyt, Perera, and Kauvar, 1941, Schaefer and Sanders, 1942) Marked tenderness of the scalp was present in our Case 2, and was reported by Johnson, Harley, and Horton (1943) and Schaefer and Sanders (1942) This tenderness in our Case 7 was so extreme at times that she was unable to rest her head upon her pillow

Horton, 1943) may show fairly good recovery, though usually once the changes have appeared some impairment is permanent. In some cases with loss of sight the fundus may appear normal at the time. From the varying types of eye symptoms and signs it seems probable that the disease process must affect the arterial supply of the optic and oculomotor nerves, and the retina in varying degree, sometimes with complete thrombosis of the affected vessel, and at other times cutting down the blood supply by temporary swelling of the vessel wall and later allowing eventual restoration of function, providing the degree of ischaemia has not been too great.

*Arteritis* Active inflammation of the temporal artery is striking because of thickening and reddening along its course (Plate 5, Fig 16). Good photographs have been published by Sprague and MacKenzie (1940) and Bowers (1940). At this stage pulsation is usually absent, but with subsidence of inflammation may return (Schaefer and Sanders, 1942, Horton and Magath, 1937, Jennings, 1938). The area of redness in the temples may suggest suppuration to the patient so that he applies poultices (Cases 3, 4, and 5). Cases 5 and 7 demonstrated that tenderness along the course of the arteries of the scalp can be present for some months prior to complete occlusion. The portions of the various arteries involved may be quite localized, so that the scalp may show one or more strictly limited areas of tenderness. With extensive involvement of the scalp arteries the skin may break down (Cases 2 and 6). Enlarged cervical glands have been noted frequently, sometimes with no obvious reason other than the inflamed arteries. It is surprising that there are not more reports of lesions of peripheral vessels. Horton and Magath (1937) reported involvement of the radial artery, and Jennings (1938) diminished pulsation of the arteries of the left arm and right foot. Extensive arterial disease was present in our Case 3, probably including the vessels of the thigh, whilst both the axillary veins and the femoral vein were involved. In Cases 1, 3, and 5 intermittent claudication was present simultaneously with the general muscle discomfort. Case 6 presented a localized and tender thickening along the right radial artery.

*Reflexes* There is no mention of alteration of reflexes in the reported cases. In our Case 3 the right supinator reflex, the abdominal reflexes, and left ankle jerk were absent. Neuralgic pains are of course common. The pains in Case 3 resembled those of brachial neuritis and anterior crural neuritis. Case 5 suffered from persistent neuralgic pains in the legs. The causation in each case seems to be similar to the temporal neuralgia arising from the inflamed arteries, and except for our Case 3 there appears to be little evidence for the diagnosis of neuritis.

#### *Blood-pressure and Laboratory Findings*

The figures for the blood-pressure, temperature, red-cell count, haemoglobin, and white-cell count are given in Table II. In nearly all cases pyrexia had been present at some time. Moderate anaemia with a slight leucocytosis was usually present. Eosinophilia has not been recorded except

between the episodes. Whilst the left fundus showed mild oedema and several small haemorrhagic extravasations, no local cause could be seen in the right eye. Their third patient's illness started with stiffness of the vertebral column, malaise, loss of weight, and anorexia, followed by temporal arteritis. Four months later she noted two small scotomata before her right eye, gradually enlarging during the day so that the next morning there was a large central scotoma. 'In a few seconds the eye was completely blind, and remained so.' Two weeks later after intravenous typhoid vaccine she felt that there had been partial loss of vision in her left eye. Examination showed no vision in the right eye, in the left eye vision was 3/30. The field of the left eye showed a superior arcuate scotoma, which began at the upper margin of the normal blind spot, and covered the entire superior nasal quadrant. Examination of the fundus of the right eye revealed a rather pale disk with slight oedema on the nasal side. There was an area of localized oedema of the retina between the disk and the macula. The fovea appeared slightly reddened, and was suggestive of a residual cherry-red spot. The lower nasal retina appeared ischaemic. The optic disk of the left eye showed one diopter of oedema and the lower temporal quadrant of the disk appeared rather pale. The veins were engorged. Scott and Maxwell (1941) have also reported a case with loss of vision in the right eye and diminished vision in the left, while in Johnson's (1943) case there was complete loss of vision in one eye. Post and Sanders (1943) described eye changes in a case diagnosed by MacDonald and Moser (1937) six years previously. The retinal arteries showed marked sclerosis with irregularity in calibre and thickening of the walls, approaching the 'copper wire' state. They noted areas of sheathing where the arterial wall appeared to have undergone a fusiform thickening which was deep red in colour with impaired light reflex and disappearance of the blood column in these areas. Below the macula were three confluent areas of silvery exudate, with no haemorrhages or signs of inflammation. They considered the picture unusual, and not that usually associated with arteriosclerosis and hypertension.

The ophthalmoscopic findings in our cases are given in detail in the appendix. Three patients became totally blind, one lost the sight of one eye, and one suffered a transitory bilateral amaurosis and subsequent constriction of the fields of vision with some optic atrophy. Case 6 showed a somewhat similar appearance to that described by Post and Sanders (1943). Diplopia has been recorded in three cases, and in three of our patients, in addition to weakness of the extra-ocular movements of the eye in two other reported cases. Ptosis was noted by Murphy (1942) and in our Case 1 for 24 hours only. There are thus at least 18 cases in which there was some visual disorder. The loss of sight may be variable in its development, sudden or extending over a period of several weeks. Both eyes may be affected simultaneously or after a long interval. The extent of the loss varies from mistiness of vision and different patterns of field defects to complete loss of sight. Even moderately severe loss for as long as five days (Johnson, Harley, and

in Case 5 The blood-pressure readings are variable, but very high readings are notably infrequent Few observations have been made on the cerebrospinal fluid. This may be normal, as in the cases reported by Horton and Magath (1937), Hoyt, Perera, and Kauvar (1941), and our Cases 5, 6, and 7 In three of our cases and in the case reported by Schaefer and Sanders (1942), the protein content has been raised without any increase in the cell count Case 1 had 130 mg per 100 c c, Cases 2 and 3, 70 mg per 100 c c, while Schaefer and Sander's case had a positive Pandy test with a Lange curve 4444444321 The Wassermann reaction has been negative in the blood and cerebrospinal fluid in all cases in which it was determined, and in all our cases

### *Pathology*

Horton, Magath, and Brown (1934) considered the histopathological picture as one of chronic periarteritis and arteritis They noted infiltration of round cells in the adventitia around the vasa vasorum, and to a slight extent in the media of the vessels Haemorrhage was present in some regions in the media The basal portions of the artery appeared acellular and there were superimposed cellular layers, which indicated that intimal proliferation had taken place in various stages They considered that the lesion probably began as a periarteritis in a small segment of a vessel and, with continuation of the process, spread to the media and intima Other writers have tended to follow this original description MacDonald and Moser (1937) noted hypertrophy of the muscular wall of the vasa vasorum with some round cell infiltration A considerable increase in eosinophile infiltration has also been noted (Bowers, 1940, Scott and Maxwell, 1941, Hoyt, Perera, and Kauvar, 1941) Sproul (1942) in his case which came to autopsy found extensive caseous necrosis of the media of most of the large arteries, which he considered were the only vessels involved The adventitia though thickened over the carotid arteries showed only minimal thickening and mononuclear infiltration Plaut (1942) considered that only a few of the giant cells could be regarded as foreign body giant cells formed under the stimulus of fragmentation of elastic laminae Gilmour (1941) reported four cases under the name giant cell arteritis He drew attention to the similarity between his cases, which showed generalized arterial involvement, and those of temporal arteritis, and considered that they were essentially similar The clinical picture in his Cases 2, 3, and 4 appears to justify this conclusion, but the identity in Case 1, a young woman of 23 years, is not so apparent She presented a ruptured subclavian aneurysm and also had a miliary tuberculous process in the cervical glands Though tubercle bacilli were not demonstrated histologically, the case appears to be more analogous to cases of tuberculous arteritis as reported by Thompson (1928) The histological changes in the remaining three cases are similar to those which we have found He considered, however, in contradistinction to other writers, that the lesion started in the media and invaded the adventitia secondarily, but all his illustrations show adventitial reaction, whilst in some cases the media shows little change



in Case 5 The blood-pressure readings are variable, but very high readings are notably infrequent Few observations have been made on the cerebrospinal fluid This may be normal, as in the cases reported by Horton and Magath (1937), Hoyt, Perera, and Kauvar (1941), and our Cases 5, 6, and 7 In three of our cases and in the case reported by Schaefer and Sanders (1942), the protein content has been raised without any increase in the cell count Case 1 had 130 mg per 100 c c, Cases 2 and 3, 70 mg per 100 c c, while Schaefer and Sander's case had a positive Pandy test with a Lange curve 4444444321 The Wassermann reaction has been negative in the blood and cerebrospinal fluid in all cases in which it was determined, and in all our cases

### *Pathology*

Horton, Magath, and Brown (1934) considered the histopathological picture as one of chronic periarteritis and arteritis They noted infiltration of round cells in the adventitia around the vasa vasorum, and to a slight extent in the media of the vessels Haemorrhage was present in some regions in the media The basal portions of the artery appeared acellular and there were superimposed cellular layers, which indicated that intimal proliferation had taken place in various stages They considered that the lesion probably began as a periarteritis in a small segment of a vessel and, with continuation of the process, spread to the media and intima Other writers have tended to follow this original description MacDonald and Moser (1937) noted hypertrophy of the muscular wall of the vasa vasorum with some round cell infiltration A considerable increase in eosinophile infiltration has also been noted (Bowers, 1940, Scott and Maxwell, 1941, Hoyt, Perera, and Kauvar, 1941) Sproul (1942) in his case which came to autopsy found extensive caseous necrosis of the media of most of the large arteries, which he considered were the only vessels involved The adventitia though thickened over the carotid arteries showed only minimal thickening and mononuclear infiltration Plaut (1942) considered that only a few of the giant cells could be regarded as foreign body giant cells formed under the stimulus of fragmentation of elastic laminae Gilmour (1941) reported four cases under the name giant cell arteritis He drew attention to the similarity between his cases, which showed generalized arterial involvement, and those of temporal arteritis, and considered that they were essentially similar The clinical picture in his Cases 2, 3, and 4 appears to justify this conclusion, but the identity in Case 1, a young woman of 23 years, is not so apparent She presented a ruptured subclavian aneurysm and also had a miliary tuberculous process in the cervical glands Though tubercle bacilli were not demonstrated histologically, the case appears to be more analogous to cases of tuberculous arteritis as reported by Thompson (1928) The histological changes in the remaining three cases are similar to those which we have found He considered, however, in contradistinction to other writers, that the lesion started in the media and invaded the adventitia secondarily, but all his illustrations show adventitial reaction, whilst in some cases the media shows little change



beyond fibrosis and capillary formation. He also noted in the larger arteries 'collapsed layers' of elastica, thought to be due to degeneration of muscle fibres, though an alternative explanation might be reduplicated layers of the internal elastic laminae

The histopathological findings in six of our cases are given in detail in the Appendix. From these, it appears possible to construct the course of the disease process in the vessels, forming a graded sequence of changes. The reaction is of inflammatory type and appears to start in the adventitia (Plate 1, Fig 1). The inflammation is subacute and subsequently spreads to the media where it tends to spread in an axial direction specially in the larger vessels. Prior to this stage, however, there is some focal necrosis affecting parts of the media and internal elastica (Plate 1, Figs 2 and 3). This area of necrosis is marked by an absence of inflammatory reaction and would correspond to a nutritional defect such as might result from occlusion of the vasa vasorum. In many cases it seems probable that the process is halted at this stage of periarteritis and focal medial necrosis with healing subsequently takes place (Plate 3, Fig 11). In most vessels the inflammatory process spreads to the media where the necrotic media and elastica sometimes excite a giant cell reaction (Plate 3, Figs 9 and 10). Surviving fragments of elastica give rise to new internal laminae (Plate 4, Fig 14). In the course of this new formation of elastica loops of elastic tissue can be seen arising near the site of the original lamina and extending into the deeper layers of the intima where the new laminae are coming into being. The inflammatory reaction may stimulate this elastic tissue formation. Such a conclusion would be justified in view of the recognized reaction of arteries to other forms of chronic inflammation. Meanwhile the media has been largely converted into chronic inflammatory granulation tissue, infiltrated by lymphocytes, plasma cells, and large mononuclears. The palisade formation of the loops of elastic tissue (Plate 4, Fig 15) arising from the site of the original lamina, tends to segregate the granulation tissue into islands, lending a superficial resemblance to tubercle follicles (Plate 1, Fig 4), an appearance which is further enhanced by the occasional presence of giant cells and collections of pale cells of reticulo-endothelial type. The latter, however, are so closely associated with the new elastic tissue that they may well be concerned with its formation. It should be stressed that this cellular reaction apparently follows the focal necrosis of the media, unlike tuberculosis where the reaction comes first and necrosis follows. Giant cells are not a constant feature in these 'follicles', and they may be found in the absence of 'follicles' when it can clearly be demonstrated that they are engaged in phagocytosis of necrotic debris (Plate 3, Figs 9 and 10). Repeated examination has failed to reveal any sign of tubercle bacilli. The intima always shows a marked thickening, and a broad band of loose cellular tissue is formed. The cells of this tissue are mainly long spindles, and the characters of some suggest that they may be derived from smooth muscle. This intimal tissue rarely shows any signs of inflammation. When it does, the reaction is in the form of a focal exten-

sion from the media. In the case of the smaller arteries these changes are usually followed by thrombosis, which appears to be rapidly organized. Thrombosis is not quite so common in larger vessels.

The arterial lesions most likely to be confused with temporal arteritis are periarteritis nodosa and thromboangietis obliterans, and many authors have found it impossible to make the distinction, especially between the latter condition and temporal arteritis. In some of our specimens the distinction has been impossible on present criteria. Nevertheless, certain generalizations may be made. Periarteritis is usually a disease of the visceral arteries, although occasionally found in the superficial and retinal vessels. The reaction is of acute inflammatory character, and the necrosis of the vessel wall tends to be of a suppurative nature. In temporal arteritis necrosis is found apart from inflammation, and where inflammation is found it is rarely more than subacute. This inflammatory reaction appears to spread axially, as opposed to the focal nature of periarteritis nodosa. Thromboangietis obliterans is usually a disease of peripheral vessels and begins most often as a migrating phlebitis of superficial veins. The usual picture is not unlike that of temporal arteritis, with granulation tissue formation in the vessel wall. The inflammatory reaction involves the whole wall, whereas in temporal arteritis the internal elastic lamina appears to be the internal limit beyond which inflammation rarely spreads. Cases have been reported, however, showing inflammation involving the whole coat in temporal arteritis (Hoyt, Perera, and Kauvar, 1941, Horton and Magath, 1937).

Giant cells are sometimes found in thromboangietis obliterans, but they are more common in the thrombus than in the vessel wall. Buerger (1914) has described an early acute inflammation of the vessel wall with polymorph cell reaction, but this stage is rarely seen. Finally, the late stage of thromboangietis obliterans results in a fibrosis involving the neighbouring veins and nerves. In temporal arteritis some fibrosis is usually found in the nearby muscle in the case of the peripheral vessels, but it is not extensive. Here again the distinction cannot be made absolute in our Case 3, where there was evidence of involvement of the femoral vein with fibrosis and recanalization. Atlas (1943) has described a case of Buerger's disease in a 67-year-old woman with changes in the leg vessels essentially similar to those which we have seen in temporal arteritis.

The distinction from tuberculous arteritis is aided by the lack of obvious tuberculous lesions in the neighbourhood of the artery, absence of the tubercle bacillus from the sections, and absence of true follicle formations (Dafoe, 1925, Thompson, 1928). Tyson (1931) has described medial degeneration and thrombosis of vasa vasorum and periarterial lesions in cases of dissecting aneurysm. In none, however, are the appearances similar to those in our cases, or those reported by Gilmour (1941). In cystic degeneration of the media, a potent cause of dissecting aneurysm, areas of non-inflammatory degeneration are found in the media in association with changes in the vasa vasorum in the adventitia. Though one might expect similarities in the

pathological picture in some cases in view of the similar age incidence, we have not been able to find any reference to the presence of widespread inflammatory reaction or giant cells

To sum up, the clear cut picture in any one of these conditions is distinctive. The variations in the reported cases and the absence of any strict criteria of differentiation sometimes make a definite histopathological diagnosis very difficult

### *Aetiology*

The aetiology of temporal arteritis is as yet unknown. Dick and Freeman (1940) suggested that the invariable presence of fever and inflammation and the self-limiting course of the disease point to an element of infection, which, being superimposed on arteriosclerosis, leads readily to thrombosis. Cultures of resected arteries in five cases by Horton and Magath (1937) gave negative results. Similar attempts by other workers have not yielded any significant findings. In none of our cases have we been able to demonstrate organisms in the sections. The hypothesis of Horton and Magath (1937) is that 'The advanced age of the patients suggests that these changes in the arteries may be one of the fruits of senility. The changes might even be brought about by small infarcts in the vascular wall due to thrombosis of the vasa vasorum.' To those who have observed the inflamed appearance of the temporal artery this hypothesis makes little appeal. Other evidence of an inflammatory process in the records we have made appears to be undeniable, but we have found no clue to the cause of this inflammation. The factors producing thrombosis, whether due to deficiencies in the blood-vessel wall or due to infection, still remain to be determined.

### *Differential Diagnosis*

From consideration of the varied symptoms presented it is clear that temporal arteritis can simulate a number of conditions, such as cerebral tumour, secondary carcinoma of the brain, cerebral vascular accidents, retinal artery thromboses of varied aetiology, sinusitis, dental neuralgia, trigeminal neuralgia, neuritis, osteoarthritis of cervical spine, fibrositis of the scalp and other tissues, and inflammation of the scalp. The severe muscle tenderness that is sometimes experienced may simulate dermatomyositis, and with the joint swellings, rheumatoid and infective arthritis must be considered. In all these instances the clinical course, or the pathological findings, eventually make the diagnosis clear.

It is in relationship to diffuse vascular diseases that difficulties in diagnosis arise. A comparison between the clinical features of temporal arteritis, periarteritis nodosa, and thromboangitis obliterans has been made in Table III. The pathological differentiation between these diseases is not always easy, though there do appear to be differences in the majority of cases. In some clinical cases, too, the distinction may not be clear. For

example, retinal artery thrombosis may occur in each condition. Retinal phlebitis has been noted in temporal arteritis and in thromboangitis obliterans. Maul (1938) reported the case of a 57-year-old man who developed thrombosis of the central retinal artery and had also Buerger's disease of the extremities. Similarly, the case of a 67-year-old woman reported by Atlas

TABLE III

*Comparison of Clinical Features in Temporal Arteritis, Thromboangitis Obliterans, and Periarteritis Nodosa*

	Temporal arteritis	Thromboangitis obliterans	Periarteritis nodosa
Sex	Twice as common in women	Almost entirely confined to men	Much commoner in men
Age	Over 55 years	Between 25 and 45 years	Usually young adults
Chronic diffuse myalgia	Frequent	Uncommon	Frequent
Joint swellings	Frequent	Uncommon	Frequent
Intermittent claudication	Frequent	Frequent	Noted
Gangrene	Not reported	Frequent	Occasionally
Headaches	Common and severe	Not prominent	Not prominent
Pyrexia	Present	Present	Prominent
Polyneuritis	Not described	Not described	Frequent
Peripheral vascular signs	Arterial thrombosis common Aneurysm not noted	Superficial and deep thrombosis of veins and arteries of legs	Nodular swellings with occasional formation of aneurysm
Albuminuria	Not described	Occasionally	Frequent
Ocular and oculomotor disorders	In half the cases	Rarely	Rarely
Prognosis	Frequently self-limiting over 6 to 12 months	Loss of limb and sometimes life	Usually fatal within a year

(1943) as a case of Buerger's disease might well fall into the category of temporal arteritis.

In general, the points set out in Table III give a number of differences which should enable a clinical diagnosis to be made. Finally, generalized arteriosclerosis complicated by cerebral symptoms, intermittent claudication, and hypertension present pictures which may be simulated or aggravated by temporal arteritis.

### *Prognosis*

Horton and Magath (1937) considered that the prognosis was good, their patients were never dangerously ill, and the total duration of illness varied from four to six months. Two of their patients died, one 12 months later, and another two years later, of conditions which were considered unrelated to their original illness. Complete recovery occurred finally in all the cases of which they had records. Subsequent writers have on the whole substantiated this favourable outlook. Thus, only two autopsies have been reported. The length of illness in Sproul's (1942) case was approximately 10 weeks after the temporal artery thrombosis. The patient reported by Chasnoff and

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Vorzimer (1944) died after 14 months of illness. The average duration of illness is, however, much longer than three to six months. Hoyt, Perera, and Kauvar (1941) found symptoms present up to two years after the onset in two of their patients. Post and Sanders (1943) have published the final result in a case observed by MacDonald and Moser (1937). The original illness lasted 12 months and the patient died six years later of a cerebrovascular accident, having been comparatively well in the interval, though suffering from a poor memory and giddiness for the last two years of her life. Of our seven cases Case 1 died six months after the onset of his illness, probably on account of cerebral haemorrhage or thrombosis. Case 3 died 30 months and Case 6 14 months after the onset. In both the disease process was still active. Of the four living cases only one is entirely well two and a half years after the onset, one is completely blind three and a half years later, though otherwise well after an illness lasting 10 months. Case 5 is incapacitated by severe arterial obstruction of his legs, so that he is confined to bed. Case 7 is still in hospital. Thus, though experience from the literature shows that the process is frequently self-limited, the generalized nature of the disease, occurring in elderly patients, makes prognosis uncertain.

#### *Treatment*

The treatment in our seven cases has been essentially symptomatic. In six of the cases biopsy on the temporal artery has been carried out, both for diagnostic and therapeutic purposes. In every case this procedure produced a diminution in the severity of the headache, such that it could then be easily controlled by analgesics. Case 5 experienced such complete relief from his right temporal headache that he asked for exploration of his occipital region. This also was done, and although the occipital artery was not actually located, a measure of relief was obtained. The results of arterial resection in our cases are similar to the good effects noted by Horton and Magath (1937), Bowers (1940), MacDonald and Moser (1937), and others. We have also used nicotinic acid 300 mg daily in some cases, and considered that it had some beneficial effect, presumably due to the vasodilator action. Potassium iodide in large doses has also been claimed to produce symptomatic improvement. Bowers (1940) found some benefit from thiamine 2 to 5 mg daily intramuscularly.

#### *Discussion*

Lack of knowledge of any aetiological factors in the diffuse vascular diseases precludes any final evaluation of the symptom complex reported under the term temporal arteritis. Nevertheless, there is a striking similarity in the reports that have been accumulating over the past 14 years of the age incidence, incapacitating headache, widespread affection of the muscles and joints, and the usually self-limiting course. Until now the term temporal arteritis has been understood to refer, as is natural, to the disease as it affects the temporal artery only, but if, as we have shown, a widespread affection

of arteries is commonly present in this disease, more differentiation will be necessary in the future to distinguish it from thromboangitis obliterans and periarteritis nodosa occurring in the later age groups. There is still relatively little known about arterial diseases. Clinical and histopathological diagnoses in the literature show much variation and overlap. Until recently biopsy observations in temporal arteritis have been unsatisfactory, various authors have described their individual cases, but at different stages of the disease, so that a clear conception of the pathological process has been impossible to obtain. Until many more autopsies have been carried out, little progress can be made. The frequency of the condition is probably much greater than has been supposed. Three further cases have been diagnosed by two of our ophthalmic colleagues since we have been aware of the disease during the past 18 months. We ourselves have under observation three further patients with visual disorders, transitory mental confusion, joint and muscle pains, headaches, loss of weight and an apparent self-limiting course, but without temporal arteritis, in whom it has not been possible to make an unequivocal diagnosis. While the gross appearances at autopsy in our third case were striking, those in our sixth case might have raised no comment. The appearances were similar to those of generalized arteriosclerosis, and only the clinical history and the histological findings gave the correct diagnosis. Gilmour (1941) described his cases as giant cell arteritis. Such a designation is unsatisfactory in that giant cells are, in the main, non-specific and are seen in a number of vascular diseases. We believe then that it will be useful to retain this group as a distinct clinical entity until further observation proves or disproves the relationship to other vascular diseases. For these reasons we have retained the term temporal arteritis, and not adopted a name signifying the more general involvement of the arterial system. Finally, we would emphasize the frequency of visual disturbances in this disease, which often results in the patients coming first under the care of the ophthalmologists.

#### *Summary*

1 The case histories of seven patients with temporal arteritis are presented. The symptoms and signs, together with those from the 31 cases reported in the literature, are described.

2 The characteristic clinical features are anorexia, loss of weight, joint and muscle pains, pyrexia, painful arterial thrombosis, and severe headaches, occurring in elderly patients. At least half the patients so far reported have had visual disturbances leading in many instances to complete loss of sight.

3 Post-mortem examination was carried out in two cases. A characteristic histological picture was noted in the aorta, temporal, radial, subclavian, femoral, coronary, renal, retinal, coeliac, and mesenteric arteries. Involvement of the femoral vein was found in one case.

4 The pathological features are those of a subacute inflammation spreading probably by the vasa vasorum to the media. The internal elastic lamina appears to cause the inflammation to spread longitudinally. The lamina may



be destroyed and in the process of healing new reduplicated layers are formed. The intima becomes hypertrophied and thrombosis is a common sequel.

5 The prognosis is relatively good as regards life, though with the generalized nature of the disease process it may be fatal in some cases.

6 Though the generalized character of the disease is emphasized, the term temporal arteritis has been retained as indicating a specific clinical entity in the absence of any definite aetiological factor.

We wish to thank Mr Beatson Hird (Honorary Ophthalmic Surgeon, Birmingham United Hospital) for his help and interest.

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## APPENDIX

### Case Reports

*Case 1* A man, aged 66 years, Insurance Agent. Admitted on 26.11.41 to the Queen Elizabeth Hospital complaining of loss of vision in the left eye, and weakness of the arms. He had always been of a nervous disposition. About 20 years previously he had had an ill-defined illness characterized by

shakiness of his arms and legs, which was thought to be organic in nature at the time. Since then some tremor of arms and legs had been present on excitement or anger. He had otherwise been well until three months prior to admission, when he began to get severe continuous frontal headache. This had begun with marked tenderness over the left side of the forehead, which was reddened. He treated it with hot poultices. One to two weeks later he developed pain in his arms and legs, and also cramp-like pains in the calves when walking, relieved by rest. He became easily tired. The headache decreased and he appeared to be improving until one month prior to admission, when on retiring to bed both his eyes closed, and he could not open them voluntarily. If he raised his eyelid with his fingers he found that he could see normally with the right eye, but the left appeared as though there was a 'black stream' falling over the eye. There was no unconsciousness, increase of headache, or other symptom of intracranial haemorrhage. He was able to stand and walk normally at this time. The vision tended to improve slowly, so that he thought it would be fully restored. However, just before admission the right side of the forehead became tender, and within 24 hours the left eye became totally blind.

On admission he looked older than 66 years. His temperature rose daily to 99° F. Both temporal arteries were thickened and tender. The radial and brachial arteries were unduly thickened. There was no pulsation in the dorsalis pedis or posterior tibial arteries. The heart, lungs, and abdomen appeared normal. The blood-pressure was 130/80. The cranial nerves, with the exception of the left optic nerve, appeared normal. His arm reflexes were very brisk, with some diminution in muscle power in all groups. There was coarse tremor of the outstretched hands and inco-ordination of cerebellar type on performing the finger-nose test. The abdominal reflexes were absent. The leg reflexes were exaggerated with flexor plantar responses and inco-ordination of cerebellar type. Sensation to pinprick and vibration sense were normal.

Mr Beatson Hird reported on the eyes: 'There has been a vascular block in the left eye, the disk is blurred and pale, the veins very engorged and compressed by the crossing arteries. No haemorrhage. A patch of exudate above the macula. The arteries are of normal size. I think he had probably an angospasm rather than a thrombosis. There is no light perception, and nothing can be done to restore vision now.' A blood count showed red cells 4,790,000 per c mm, haemoglobin 96 per cent, and white cells 11,850 per c mm, with 72 per cent polymorphonuclears. The cerebrospinal fluid was under normal pressure, and contained protein 130 mg per 100 c c, but no increase in cells. The Wassermann reaction in both blood and cerebrospinal fluid was negative.

The patient was treated with rest and sedatives. His temperature rose occasionally to 99° and 100° F. At times his headache was severe. After ligation and removal of parts of both temporal arteries, his headaches almost disappeared, and he was discharged home to continue convalescence. Six weeks after discharge he died suddenly, the description of his death suggested a cerebral vascular accident.

*Histological report on sections of artery.* 'The vessel was embedded in dense fibrous tissue and showed a mild periarteritis in the form of a lymphocytic and plasma cell infiltration. The media showed no change, but it was separated from the internal elastic lamina by an irregular space containing granular debris and a few multinucleated giant cells. The intima was thickened' (Plate 1, Fig 1)

*Case 2* A married woman aged 66 years. This patient had been previously healthy. In February 1942 she sustained a fall, and shortly afterwards began to lose weight, became easily tired, and had a very poor appetite. She was admitted to another hospital for investigation for diabetes, which was not confirmed. Shortly after discharge from hospital, she complained of tenderness and aching of the back, spreading upwards to the head. It became so severe and universal that she was hardly able to bear being touched. At this time she considered that her eyesight was not quite as good as usual when sewing, but the impairment was slight. About three months after the onset of her illness she began to have severe headaches and to develop excessive thirst and polyuria. The headaches continued, and three weeks later for a period of three to four days she had diplopia, the right sided image being beside and slightly above the image of the left eye. At the end of this time she noticed that the sight of the right eye diminished rapidly, and she became totally blind in 24 hours. She described the process as being 'like a cloud passing in from the side and gradually shutting out all the light' from temporal to nasal side. From this time onwards until she was admitted to the Queen Elizabeth Hospital one month later, she had severe pain in her face so that she had difficulty in opening her mouth. Tenderness was specially marked over the right temporo-mandibular joint. About two weeks before admission severe tenderness over the scalp appeared. This was shortly followed by swellings which came up like blisters and broke down, the affected area being very tender. One week prior to admission she noticed that the sight of the left eye was becoming affected, so that objects in the temporal field could not be seen.

Examination on admission to hospital (8.8.42) showed no abnormal findings in the heart, lungs, or abdomen. The blood-pressure was 130/75, and the pulse rate 75. The patient was well orientated, and able to give a clear history. She was moderately well nourished. The scalp was covered with a number of vesicles and much crusting. It was tender specially over the right temporal region. The cranial nerves, except the second, and arm and leg reflexes were all normal. Examination of the right eye showed a rather dilated pupil with no reaction to light or accommodation. There was a small flame-shaped haemorrhage above and nasally to the disk, and two large patches of oedema and whitish exudate inferotemporal to the disk. The arteries were contracted. The disk margin was blurred and showed papilloedema. The disk appeared paler than normal. There was only perception of light. The left eye showed the presence of mild papilloedema and pallor of the disk, but the changes in the remainder of the fundus were not remarkable. The pupil did not react to light or accommodation. There was diminution of the temporal field of vision.

A blood count showed red cells 3,620,000 per c mm, haemoglobin 70 per cent, and white cells 10,700 per c mm, with 78 per cent polymorphonuclears. The bleeding time was 7.5 min and initial clotting time 12 min. A fractional test meal showed the presence of free hydrochloric acid. Lumbar puncture showed an initial cerebrospinal fluid pressure of 196 mm. The fluid showed no increase in cells, but contained 70 mg per 100 c c of protein, with a normal Lange curve and a negative Wassermann reaction.

Observation over 12 weeks in hospital showed that she had an occasional temperature of 99.6°F, but that in the main she was afebrile. Her pulse remained constantly around 80. Three days after admission it was noted that she had lost perception to light in both eyes, and since that time she has remained totally blind. She suffered a severe vaginal haemorrhage shortly

after admission, but examination by a gynaecologist did not reveal anything abnormal in the pelvis. The lesions of the scalp involved the whole head, but slowly reacted to treatment with sulphonamide and starch compresses, although even after 12 weeks an extensive area of the scalp was still unhealed. Examination of the eyes three weeks after admission by Mr Beatson Hird showed complete loss of sight. The circulation in the arteries had been to some extent restored, but optic atrophy was commencing in both eyes. Three months after her admission both disks showed atrophy. The arteries, especially those on the left, were extremely thin and of uneven calibre. Inquiries by letter to her doctor 36 months later elicited the reply that her general health had remained good, that she was still completely blind, and that the lesions on her head still tended to break down. Whilst in hospital, the diagnosis of temporal arteritis had been made. It proved impossible to find any artery on the scalp owing to the extreme degree of infected seborrhoea. A muscle biopsy from the back was taken, but beyond revealing some degree of muscle atrophy did not show any change in the vessels.

*Case 3* A woman aged 69 years. This patient had been perfectly healthy until November 1941. She then developed pain and gradually increasing stiffness in the right thigh, with some numbness and wasting. Shortly afterwards the left thigh was similarly affected. Two weeks later she developed pain on the internal aspect of the right arm, which became swollen so that she was unable to use it. The condition cleared up slowly, and she also had pains in the right deltoid region and across the shoulders. She was confined to bed during this period for approximately six months. When first seen in February she had apparently only a simple right axillary vein thrombosis. Shortly after this the left axillary vein was similarly affected, but cleared up comparatively rapidly, and she was well for a few weeks. In June she began to have severe headache. Ten days later she had diplopia for two days, and vomited on two occasions. On questioning later she admitted that during this period she had had a blue and painful swelling on her left temple. After the diplopia she stated that a fog seemed to come in front of the left eye, and then a veil seemed to close in front of the eye from the side. She then found that she was blind in the left eye, papilloedema of the left disk was noted by her doctor. The headache continued and she noted a similar blue and very painful swelling on her right temple. Two weeks later she experienced exactly the same symptoms in the right eye, and became almost totally blind.

Examination then showed that both the disks were swollen and pale, pallor being most marked on the left. There was no retinitis, and the arteries appeared normal. The left eye was blind, whilst the right eye was able to distinguish fingers. The cranial nerves were normal. The reflexes in the arms showed an absence of the right supinator jerk and weak triceps jerks on both sides. The abdominal reflexes were absent. The knee-jerks were brisk and equal, whilst the left ankle jerk was absent and the plantar responses flexor. Vibration sense was present in the arms and legs. Pinprick sensation was normal except for slight blunting on the right forearm and hand. Her tongue was reddened and showed mild glossitis. There was a little oedema of both feet. Her blood-pressure was 190/105. The urine contained no albumen or sugar. There was good pulsation in the dorsalis pedis and posterior tibial arteries.

Her condition remained unchanged until admission to the Queen Elizabeth Hospital (26.7.43), when the following additional features were noted. General

muscular weakness in the arms and legs, perhaps most marked on the right leg. The legs were stiff, and there was some peri-articular swelling of the knee joints. Her mental powers were so poor that it proved difficult to get any consistent history, and the patient herself complained of her increasing loss of memory. Both temporal arteries were noted to be thickened, slightly reddened, and still very tender. She complained of little headache. Examination of the eyes by Mr. Beatson Hird at this time showed that the pupils did not react to light or accommodation. The right eye showed optic atrophy with slight blurring of the disk. The arteries were contracted with some degenerative changes. The left eye showed similar findings. He concluded that the ophthalmoscopic findings were those of a retinal artery block in each eye.

A blood count showed red cells 3,940,000 per c mm, haemoglobin 72 per cent, and white cells 5,100 per c mm, with a normal differential count. A urea clearance test showed a blood-urea of 29 mg per 100 cc and urea clearance 90 per cent of normal. The Wassermann reaction was negative in the blood. A biopsy of both temporal arteries was made. Both arteries showed similar appearances. A slight lymphocytic reaction was found in the peri-arterial coat. The media showed numerous 'windows' of atrophy in which lymphocytic and plasma cell reaction were noted. Only small fragments of the internal elastic lamina remained. Around these fragments were 'follicular' structures composed of pale cells with large pale nuclei, and multinucleated giant cells. Lymphocytes and occasional polymorphonuclears were also present, the latter mainly in relation to areas of necrosis. New layers of elastic tissue had been formed on the inner aspect of these follicles, and internal to these new layers of elastica was a zone of chronic inflammatory reaction confined to the deeper layers of the thickened intima.

She was kept under observation for four months in the Queen Elizabeth Hospital, during which time she was afebrile. Her mental condition gradually deteriorated and at times she was completely irrational and disorientated. Her general condition grew weaker. She became incontinent of urine and faeces, and her urine became infected. She was transferred to a hospital for the chronic sick to continue under supervision. Here she was given nicotinic acid 200 mg daily, and after six weeks' therapy her mental and general condition improved so that she seemed fully aware of her surroundings and was only occasionally incontinent of urine and faeces. Her condition then remained unchanged until her death in April 1944, approximately two and a half years after the onset of her illness.

*Post-mortem examination.* The body was that of an elderly woman of average build. There were several papery scars with slight surrounding pigmentation on the outer surface of the left buttock. Several pressure sores were present on the posterior surface of the right buttock and over the right great trochanter. There was some excoriation on the inner surface of the thighs. The ankles were moderately oedematous.

*Cardiovascular system.* The heart (600 gm) showed no external abnormality other than a small milk-spot over the right ventricle. There was some hypertrophy of the left ventricle, but the muscle was of good quality. The valves were normal apart from slight senile thickening of the mitral valve. Small patches of apparent atheroma were present along the branches of the coronary arteries. Just above the aortic ring the aorta showed a mild degree of aneurysmal dilatation. Five and a half cm above the ring on the anterior wall of the beginning of the arch, at the point of origin of the right innominate artery, there was a raised rough area polygonal in shape (6 × 3 cm).

The surface of the aorta over this area was covered by granular yellowish-grey material suggesting a fibrinous clot. The first part of the right subclavian and the right common carotid arteries showed no abnormality. At the bifurcation of the latter vessel there was a small area of calcified atheroma, but the surface was intact. The left common carotid artery was atheromatous. At the origin of the left subclavian artery there was another area, 1.7 cm in diameter, similar to that described in the first part of the aorta. Just distal to the left subclavian artery there was another similar lesion on the posterior aspect of the aorta, which was cut on opening the vessel. It was in the form of a longitudinal strip 10 cm  $\times$  1.7 cm. On removing this yellowish-grey material from the surface of the aorta, it left a rough red line of cleavage. Further lesions of a similar nature were present in the abdominal aorta, one on the left lateral aspect at the level of the diaphragm, 3.5 cm in length, others smaller in size lower down. The lower part of the abdominal aorta also showed calcified atheroma. The renal arteries showed no significant change. The coeliac axis and superior mesenteric artery showed no macroscopic abnormality. The right femoral artery showed a small lesion similar to those in the aorta. The pulmonary arteries, innominate veins, portal vein, inferior vena cava, common iliac veins, pelvic venous plexus, and right saphenous veins showed no abnormality.

**Respiratory system** The left pleural cavity contained 550 c.c. of clear fluid. A few adhesions were present at both bases. Both lungs were congested and moderately oedematous in the lower lobes.

**Alimentary system** No abnormality could be seen in the stomach and intestines. The liver (1,200 gm.) was of normal size and no significant change was seen on the cut surface. The gall-bladder was healthy. The spleen (300 gm.) was enlarged and pink. The diffuse colouring masked the miliary bodies.

**Genito-urinary system** The kidneys (average 200 gm.) were enlarged. The capsules stripped freely, leaving a smooth surface. A single cyst was present on the cortex of the left kidney, and both kidneys showed a few depressed cortical scars. The bladder, uterus, and ovaries were normal.

**Central nervous system** The superficial cerebral vessels were congested and the brain was somewhat oedematous. No gross abnormality could be seen in the brain substance, but there were small areas of irregular congestion, about the size of a millet seed, scattered throughout the white matter of the cerebral hemispheres and midbrain. The main vessels at the base of the brain showed scattered whitish patches which may have been due to atheroma.

Sections of all organs were examined. In addition, material was taken from the aorta, the mesenteric, splenic, renal, cerebral, both femoral and subclavian arteries. The preparations were stained by haematoxylin and eosin, Masson's trichrome method, and Verhoeff's technique for elastic tissue. The lungs showed well-marked chronic venous congestion, but were otherwise healthy, and no sign of any abnormality could be found in the walls of the larger vessels. No significant change could be found in the liver, but marked lesions were noted in the kidneys. The glomeruli were much larger than normal, and the tufts filled their capsules. Lobulation was marked and in some cases the capillary tufts projected into the first convoluted tubules. In a few cases the tufts appeared to be adherent to their capsules, and all of them showed increased cellularity, the cells being of endothelial type. The capillary walls were thickened and hyaline. The tubules showed acute degenerative changes, amounting in many instances to necrosis (Plate 4,

muscular weakness in the arms and legs, perhaps most marked on the right leg. The legs were stiff, and there was some peri-articular swelling of the knee joints. Her mental powers were so poor that it proved difficult to get any consistent history, and the patient herself complained of her increasing loss of memory. Both temporal arteries were noted to be thickened, slightly reddened, and still very tender. She complained of little headache. Examination of the eyes by Mr. Beatson Hird at this time showed that the pupils did not react to light or accommodation. The right eye showed optic atrophy with slight blurring of the disk. The arteries were contracted with some degenerative changes. The left eye showed similar findings. He concluded that the ophthalmoscopic findings were those of a retinal artery block in each eye.

A blood count showed red cells 3,940,000 per c mm, haemoglobin 72 per cent, and white cells 5,100 per c mm, with a normal differential count. A urea clearance test showed a blood-urea of 20 mg per 100 cc and urea clearance 90 per cent of normal. The Wassermann reaction was negative in the blood. A biopsy of both temporal arteries was made. Both arteries showed similar appearances. A slight lymphocytic reaction was found in the peri-arterial coat. The media showed numerous 'windows' of atrophy in which lymphocytic and plasma cell reaction were noted. Only small fragments of the internal elastic lamina remained. Around these fragments were 'follicular' structures composed of pale cells with large pale nuclei, and multinucleated giant cells. Lymphocytes and occasional polymorphonuclears were also present, the latter mainly in relation to areas of necrosis. New layers of elastic tissue had been formed on the inner aspect of these follicles, and internal to these new layers of elastica was a zone of chronic inflammatory reaction confined to the deeper layers of the thickened intima.

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latter, however, showed areas of fibrosis with the formation of new dilated capillaries. The intima was slightly thickened (Plate 4, Fig 12). The reaction in the left subclavian artery was substantially the same as that in the right, but appeared to be more extensive. The media was largely replaced by fibrous tissue in which small collections of lymphocytes and plasma cells could still be seen. Giant cells were absent. The internal elastic lamina was reduplicated and the intima was thickened. Several branches of the superior mesenteric artery were examined, and in some there seemed to be a combination of atheroma and arteritis. The adventitial tissues were infiltrated by plasma cells and lymphocytes, and the same reaction could be found in the media on one aspect of the circumference, at which point the media was greatly thinned. The intima showed general thickening, but over the area of medial thinning the thickening was enormous and the deeper layers showed atheromatous degeneration with early calcification. Sections of the arteries were stained by the methods of Levaditi, Ziehl-Neelsen, and Gram, but no bacteria could be found.

*Case 4* A man aged 71 years. This patient had been well until approximately five months prior to admission. He then began to get headaches of no severity and of no particular localization on a number of occasions. Five weeks prior to admission the headaches suddenly became more severe and continuous so that they frequently prevented him from sleeping and woke him up if he did sleep. The pain was chiefly on top of the head and extending down the back of the head to the neck behind both ears. The pain was a continuous ache without any sharp component. Nothing appeared to relieve it.

Examination on admission to the Queen Elizabeth Hospital (15.11.43) showed a healthy and young looking man of 71 years. Physical examination of the heart, lungs, and central nervous system showed no abnormality. His blood-pressure was 150/95. Palpation and movement of his cervical spine caused some pain. There were numerous tender spots in the muscles and deep fascia at the base of the neck, and on the occiput. Though the occipital arteries were palpated, they did not seem to be affected.

A blood count showed red cells 4,200,000 per c mm, haemoglobin 60 per cent, and white cells 8,400 per c mm with 52 per cent polymorphs, and 17 per cent monocytes. A lumbar puncture showed the cerebrospinal fluid to be under normal pressure and to contain 70 mg per 100 c c protein, but no increase of cells. The Wassermann reaction in the blood and cerebrospinal fluid was negative.

The patient, who was apyrexial, was observed in hospital and treated with analgesics, with very little relief. Approximately 10 days after admission, after more severe headaches than usual, it was noted that the temporal artery, though presenting pulsation below the zygoma had lost its pulsation above, and was hard and tender. Portions of both temporal arteries were excised.

Histological examination showed that both were affected. The left artery was occluded by a thrombus, which was completely organized and partially canalized. A considerable amount of fibrosis was seen around the artery and this appeared to be a replacement fibrosis of the surrounding skeletal muscle. A mild degree of peri-arteritis could be seen, but the main lesion appeared to be around the internal elastic lamina. The media was much thinned, and at one point appeared to be breached by chronic inflammatory granulation tissue from the adventitia. The original internal elastic lamina was fragmented. Around the fragments rounded collections of cells were



Fig 13) The intertubular connective tissue appeared very oedematous. No cellular reaction could be found in the interstitial tissue, apart from a few collections of lymphocytes and plasma cells near the surface of the cortex. The main renal arteries showed reduplication of the internal elastic lamina, and in some of the smaller arteries a slight lymphocytic infiltration could be seen in the medial and peri-arterial coats. The splenic sinusoids were widely dilated, and contained large numbers of reticulo-endothelial and plasma cells. The former were of two distinct types. One was a foamy cell, the other a dark cell of the Reed-Sternberg type usually seen in lymphadenoma. The plasma cells occasionally occurred in a syncytial form. A few eosinophiles were seen. Deposits of haemosiderin were seen in some of the reticulo-endothelial cells and the connective tissue. No change could be seen in the walls of the cerebral vessels apart from atheroma, but many of the smaller vessels contained ante-mortem thrombus. In some of these the condition appeared to be of embolic nature, but in others the thrombus had been formed *in situ*. The adjacent brain tissue showed signs of softening.

Little change of any significance could be seen in the heart apart from some small areas of replacement fibrosis. Of the other arteries examined marked changes were found in the aorta and femoral arteries, with less pronounced lesions in the mesenteric arteries. Beneath the ribbon-like thrombi the aorta showed an extensive inflammatory reaction which was almost entirely confined to the media. Occasional loose collections of plasma cells and lymphocytes were present in the adventitia, usually around the vasa vasorum, but this reaction was very mild compared with that affecting the media. In the latter situation the inflammatory reaction appeared to extend longitudinally and its limits were almost exactly marked by the ribbon-like thrombi. The cellular reaction consisted mainly of lymphocytes and plasma cells. At irregularly placed sites along the wall there were points of more intense reaction. In these foci the elastic fibres were destroyed and the area occupied by closely packed masses of cells, mainly of plasma and lymphocyte variety, but a few polymorphonuclears were also present. In some of these areas syncytial-like sheets of plasmacytoid cells could be seen (Plate 3, Fig 8). A few of the more acute lesions had spread into the intima, but the latter was practically free from involvement (Plate 3, Fig 10). The left femoral artery showed a peri-arterial plasma cell reaction around the vasa vasorum, and some of these vessels showed endarteritis. In some places the external elastic laminae had disappeared, and the tissue spaces were occupied by lymphocytes and plasma cells. The media was largely replaced by granulation tissue infiltrated by mononuclear cells. At some points the internal elastic lamina was destroyed, and its place taken by a column of multinucleated giant cells. The intima was thickened and a few layers of reduplicated elastica could be seen in its deeper layers. The appearances of the right femoral artery were very similar to those of the left. The adventitia was infiltrated by plasma cells and lymphocytes, especially around the vasa vasorum. This cellular reaction spread into the media, which was almost completely destroyed and replaced by fibrous tissue. Multinucleated giant cells were present. These were gathered around spicules of colourless refractile material (Plate 3, Figs 10 and 11). The internal elastic lamina was fragmented, but in this case there did not seem to be any attempt at regeneration. The intima was greatly thickened. The appearances in sections of the right subclavian artery suggested that the lesion had been of mild type and was in process of healing. The adventitial coat showed the usual inflammatory reaction, but there was no trace of any spread into the media, the

the muscles themselves Examination of the fundi showed no abnormality except slight arterial thickening

A blood count showed red cells 4,850,000 per c mm, haemoglobin 98 per cent, and white cells 10,050 per c mm, with 64 per cent polymorphs and 7 per cent eosinophiles Cerebrospinal fluid examination showed no increase of cells, with protein 36 mg per 100 c c A fractional test meal showed hyperchlorhydria An X-ray of the chest was normal with a normal sized heart, and an electrocardiogram revealed no abnormality

A small portion of the right temporal artery was removed two inches away from the tender spot on the forehead Histological examination showed some endarteritis, but no inflammatory reaction, or signs which we had previously associated with temporal arteritis After this procedure the patient experienced a striking amelioration of his headache in the temporo-parietal area, so much so that he asked for exploration of the occipital area to relieve him of the pains there This was carried out, but the artery was not located, nevertheless some relief was experienced Whilst in hospital the patient had an occasional temperature of 99°F He was discharged home after two weeks in hospital greatly improved and almost rid of his headaches After discharge from hospital his condition gradually deteriorated, and he became almost completely confined to bed, the pains in his legs being particularly severe He continued to lose weight Two weeks before his second admission to hospital, whilst having his evening meal he found that he was unable to see to eat He could appreciate light and moving objects This state persisted for 24 hours, and then gradually cleared, the left eye being more affected than the right, and in both the eyesight was blurred His headaches were rarely severe and occurred only occasionally

He was readmitted on 26.3.45 He had lost weight, weighing 8 st 9 lb The right temporal artery and its branches showed extensive thrombosis and were slightly tender That on the left showed a patchy thrombosis of a number of its branches The arms showed wasting of all muscles, especially the small muscles of the hand The reflexes were present and equal, co-ordination, sensation to touch and vibration normal The legs showed wasting and weakness Pulsation in the dorsalis pedis and posterior tibial arteries on both sides was still absent The muscles of both thighs were tender, especially along the line of the femoral arteries The pupils reacted to light and accommodation The right optic disk appeared normal and the arteries were small, but there was little evidence of arteriosclerosis Whitish subretinal haemorrhages were present in the macular region The left fundus showed very small arteries with comparatively large veins There was some oedema of the macular area The left disk was atrophic and pale, with distinct edges, and the visual fields showed some general constriction on the right and more so on the left The urine contained nothing abnormal, and a urea clearance test showed normal function The blood-sugar three hours after breakfast was 124 mg per 100 c c Biopsy of the left temporal artery confirmed the diagnosis The adventitial tissues were infiltrated by lymphocytes and plasma cells, grouped mainly around the vasa vasorum This inflammatory reaction had spread into the media, which was largely replaced by chronic inflammatory granulation tissue Giant cells of foreign-body type were engaged in removing the fragmented internal elastic lamina The intima was greatly thickened, and at one point the inflammation had invaded the deeper intimal tissues

The patient was treated with rest and diathermy to his thighs The right leg became warmer, and the pain at rest disappeared from this leg, though

gathered. These cells were well defined with large pale nuclei possessing a single prominent karyosome. The appearances thus produced were very similar to those of tuberculosis. Plasma cells and lymphocytes abounded and an occasional polymorphonuclear cell was noted. Around these 'follicles' were strands of new elastic tissue in a palisade form which joined together on the inner side to form several new lamina. The intima was greatly thickened, but little sign of inflammatory reaction could be seen (Plate 4, Fig 14). The appearances in the right artery were almost exactly the same as those in the left. In addition to the features noted above, giant cells of the Langhans type were found around the fragmented internal elastica. Examination of many sections of both these arteries failed to reveal any sign of tubercle bacilli (Plate 4, Fig 15).

He had a little relief from his headache after the operation, and over the next four weeks the headache gradually diminished, though it did not entirely disappear before his discharge from hospital. A letter from his doctor in July 1945 stated that he was well and free from pain. After discharge from hospital, he had had several slight attacks of vertigo, associated with head pains. His blood-pressure was still low.

*Case 5.* A man aged 69 years. This patient was first seen on 16.11.44 on account of severe and incapacitating headache of one month's duration. With the exception of one severe attack of lumbago four years previously, his health had been good until May 1944, when he had severe pain in the back and legs associated with joint pains and swelling of the knees and ankles. He felt generally unwell and gave up work on this account. His appetite had become poor and he had lost one stone in weight. He had suffered from cramps in the legs and some pain in the legs on walking, relieved by rest. One month before he was first seen he developed sharp, shooting, knife-like pains radiating from the left temporo-parietal region, superficial in character. There was some radiation backwards above the ear. The pains were associated with the appearance of a red, painful, throbbing spot on the left temple. The patient treated this with the application of medicated wool. After two weeks the pain suddenly ceased, but was replaced by a similar more severe pain on the right side. This was also associated with a painful red and swollen spot on the right temple. Pains then developed down the back of the neck and in the occipital region. The gums and jaw of the right side throbbed and ached intermittently, and were too tender to allow insertion of his dentures. Over the whole of this month there had been an exacerbation of his 'rheumatism', generalized aching of the upper arms, lumbar muscles, and thighs, of cramp-like character.

Examination showed a co-operative and intelligent man. He appeared somewhat wasted, weighing 9 st 10 lb. The heart, lungs, and abdomen showed no abnormality, the blood-pressure was 180/90. Examination of the nervous system showed no abnormality except that vibration sense was absent in both ankles, and postural sense defective in the left toe joints. Both temporal arteries were easily palpable. The right was tender but pulsatile. There were raised and tender spots above the right eye and also over the temporo-mandibular joint, the skin was slightly oedematous. The right occipital artery was tender and pressure caused radiation of pain up the back of the head. There was marked tortuosity of the brachial and radial arteries. Pulsation was absent in the dorsalis pedis and posterior tibial arteries. The muscles of the thighs and arms were wasted and tender to palpation, but there was no swelling of any joint or pain on movement other than that in

matory reaction in the inner part of the media around the internal elastic lamina, and also in the adventitia. Occasional foreign-body giant cells were seen in the media. The reaction appeared to involve the whole circumference, and to have spread in an axial direction. After the biopsy the patient experienced striking relief from the severe type of headache, though the generalized form remained. She appeared comfortable, but 10 days after admission had a severe attack of giddiness, followed by nausea and vomiting. She had further similar attacks over the succeeding days, but no physical sign of nervous involvement could be detected until three days after the first attack, when it was noted that the patient was totally deaf in the left ear, and partially so in the right. For the next seven days she became irrational, she was incontinent of urine and faeces, and at times difficult to keep in bed. Her condition then improved and hearing returned so that she could hear the normal voice at 2 feet in either ear. She appeared to be well orientated, though extremely querulous and still occasionally incontinent. Neurological examination at this time was still negative, whilst the cerebro-spinal fluid was under normal pressure, containing 47 mg per 100 c.c. protein, and no increase in cells. The Wassermann reaction was negative. Two weeks later she began to deteriorate again, and lapsed into coma. She died on 18.6.45, 14 months after the commencement of her illness. During her stay in hospital she was afebrile, except for a terminal rise in temperature. Autopsy was carried out 12 hours after death.

*Post-mortem examination* The subject was an emaciated elderly woman of small stature. No abnormality could be found in the pericardium. The heart (280 gm) was larger than expected. There was slight fatty change in the papillary muscles, and the ventricular wall showed flecks of fibrosis. The valves were relatively incompetent, but healthy. The aorta was extremely atheromatous, and showed several small, dark brown, thickened patches. At the site of the latter, a thickening could be felt to extend through to the peri-arterial coat. There was no sign of thrombus formation. The great vessels of the head and neck appeared normal, apart from some atheroma of their origins. Both lungs showed basal congestion and oedema, and at the apices there were old tuberculous scars, but otherwise the lungs were normal. The liver was normal. There was a considerable degree of cholesterosis of the gall bladder, and it contained a tiny cholesterol polyp. No significant change could be seen in the spleen. Both kidneys showed a mild degree of pitting of their surfaces due to vascular degeneration. The superficial vessels of the brain were congested, and an occasional small subarachnoid haemorrhage was present on the vertex. Both optic nerves showed marked softening. No marked change could be found in the mesenteric, femoral, or subclavian arteries. There was some thickening of the upper part of the radial arteries.

*Histology* In the heart there was patchy degeneration of the muscle fibres and well-marked replacement fibrosis. Lymphocytic and plasma cell infiltrations were marked in the adventitia and media of the coronary arteries. The adventitial reaction could be traced to the arterioles, but the medial infiltration was restricted to the main branches. Apart from oedema and congestion the pulmonary tissue appeared to be normal. The central cells of the liver lobules showed degeneration and shrinkage. Pigment deposition was marked and the changes appeared to be a form of brown atrophy. Reticulo-endothelial cells of the splenic pulp showed evidence of hyperplasia, but otherwise the splenic tissue was normal. The renal cortical tubules were degenerate, but the glomeruli were normal, and there was no evidence of any change in the renal vessels. In the brain tiny softenings were common in

pulsation did not reappear in the arteries of the foot. The left leg remained in poor condition with very little circulation. He was eventually discharged home to continue rest with the hope that improvement in the circulation of the left leg would occur. During the whole of his hospital stay he ran a slight pyrexia to  $99^{\circ}\text{F}$ .

*Case 6* A married woman, aged 73 years. She was admitted to the Queen Elizabeth Hospital on 5.5.45 for observation on account of loss of weight and severe headaches. She had had four healthy children, and her health had always been good until March 1944. She then began to complain of lack of energy, easy fatigability, loss of appetite, and vague generalized muscle pains. These symptoms increased, so that in August she ceased her work in a factory for a rest. In September she developed pains across the shoulders and down the arms and legs, with some swelling of the wrist joints. About the same time she complained of persistent generalized headaches of moderate severity. Her health continued to be poor and in February 1945, while crossing a street, she developed double vision, lasting for five minutes. She had no exacerbation of her headache at this time. Two days later, happening to cover her left eye, she found that she was unable to see with the right. Examination at another hospital at this time showed some swelling of the right disk, and vision restricted to perception of hand movements only. Vision in the left eye was 6/36, and the fundus appeared normal. There was, however, a slight general contraction of the visual field with a marked defect in the lower nasal quadrant. Four days after the right eye was affected, she found that she could not see anything clearly with her left eye, and nothing in the lower half of her visual field. During the next 24 hours she became totally blind. Four weeks later, and approximately eight weeks before being admitted to hospital, her headaches, which had never been completely absent, became more severe, with periodic exacerbations of sharp stabbing pains, most marked over the left temple, and frequently waking her from sleep. At the time of admission the headaches had somewhat improved. She still had some limb pains, her appetite was poor, and she had lost 21 lb. in weight since the onset of her illness.

Examination at this time showed a small co-operative woman, with marked generalized muscle wasting, weighing only 6 st. Both temporal arteries were thickened and showed thrombosis, the left being also very tender. In the scalp there were several small areas of ulceration of the skin supplied by the affected arteries. The radial artery showed in addition marked tenderness and thickening 2 in. in length just after its origin. There was good pulsation in the dorsalis pedis and posterior tibial arteries. The heart was not enlarged, the heart sounds were normal, and the blood-pressure 140/70. There was no clinical abnormality to be found in the lungs or abdomen. The nervous system, with exception of the findings relative to the eyes, showed no abnormality. The pupils were moderately dilated with no reaction to light or accommodation. There was no perception of light in either eye. In both there was a generalized corneal opacity making observation difficult. Both disks were pale and showed primary atrophy. No exudates or haemorrhages were seen. An X-ray of the chest showed no abnormality. The urine contained neither sugar nor albumin. A blood count showed red cells 3,960,000 per c mm, haemoglobin 74 per cent, and white cells 8,350 per c mm, with 61 per cent polymorphonuclears and no increase of eosinophiles.

Resection of a portion of the temporal artery showed that the vessel was completely occluded by an organized thrombus. There was a subacute inflam-

ri-arteritis with obliterative changes in the vasa vasorum. In parts the media was necrotic and thinned, and there was extension of the chronic inflammatory reaction to the intima, which was thickened. The left appeared to be an older lesion. The adventitia and media were very fibrotic. The intima was thickened, and there was still a lymphocytic and plasma cell infiltration of the outer arterial coats. The vasa vasorum showed obliterative arteritis.

On admission to hospital the patient had a temperature of 103° F. Though she fell with rest, it never disappeared, and was frequently noted to be 101° F. Her headaches were particularly severe, but after the biopsies those in the temporal areas were relieved, while those in the occipital areas persisted. She was also given nicotinic acid 300 mg daily in divided doses, with some beneficial effect. Her general condition improved gradually, though at the time of completion of the present paper she was still in hospital.

the subcortical white matter, and the related vessels showed thrombosis. Some of the thrombi contained many polymorphonuclears, but there was no evidence of any inflammatory reaction around these vessels. The appearances in the aorta were almost identical with those seen in Case 3, the same adventitial and medial infiltration of inflammatory cells spreading in the longitudinal axis of the vessel. The elastic tissue and muscle fibres were largely destroyed. There was marked atheromatous degeneration of the intima, but there was no sign of thrombosis. The right radial artery showed marked endarteritis. The media was broken up by plasma cell reaction, and the internal elastic lamina was fragmented. In parts there was evidence of healing with fibroblast activity. Some of the vasa vasorum were thickened, and almost all of them were surrounded by a cuff of lymphocytes and plasma cells. The superior mesenteric artery showed a similar inflammatory reaction with destruction of the media at the origin of the artery, but there was no sign of this in the vessels of the coeliac axis, or inferior mesenteric artery. Inflammatory reaction was present in the adventitia of the right femoral artery, but it was slight and there was no evidence of spread to the media. Both retinal arteries were equally affected. The lumen was obliterated by cellular fibrous tissue obviously formed during the organization of a thrombus. The adventitia and media were infiltrated by lymphocytes and plasma cells, and the internal elastic lamina was fragmented and calcified. A few giant cells were engaged in phagocytosis of these calcified fragments. These changes could be traced forward into the branches of each artery.

*Case 7* A married woman aged 68 years, was admitted to the Queen Elizabeth Hospital on 8.8.45 complaining of severe headache. Twenty years previously she had undergone a partial thyroidectomy, but otherwise had been well until two years prior to admission. She had then suffered from sudden transitory attacks of dizziness and recurrent mild headaches once or twice a week. These became worse and more frequent 12 months later until six months previous to admission, when she was often woken at night by the severity of the headaches which were situated in the temporal and occipital regions. She also had pains of moderate severity in her legs. Over the previous 12 months she had had little energy and a poor appetite, losing 32 lb in weight. Over the previous three months the arteries on her forehead had been tender and throbbing, and her scalp was so tender that at times she was unable to rest her head on the pillow. She had had some pain on opening her mouth, and some deterioration of eyesight.

Examination showed a thin, wasted woman weighing only 5 st 1½ lb. The arteries of the scalp were all dilated, reddened, tortuous, tender, and pulsating. Pulsation was present in the dorsalis pedis and posterior tibial arteries. No tenderness could be detected along the line of any of the arteries. The heart was not enlarged. The blood-pressure was 140/80. Examination of the nervous system showed no alteration in the reflexes, vibration sense, superficial sensation, or co-ordination. The fundi showed only slight arteriosclerosis and general narrowing of the vessels. The optic disks were normal.

A blood count showed red cells 4,380,000 per c mm, haemoglobin 80 per cent, and white cells 13,200 per c mm, with 77 per cent polymorphonuclear cells and no increase in eosinophiles. The cerebrospinal fluid was under normal pressure, containing 32 mg per 100 cc protein and no increase in cells. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The urine contained no abnormality.

Resection of both temporal arteries was carried out. The right showed a

Fig 1 Case 1 Section of temporal artery showing a chronic inflammatory reaction in the adventitia, separation of internal elastic lamina from media and giant cell formation in the resulting space ( $\times 50$ ) Stained haematoxylin and eosin

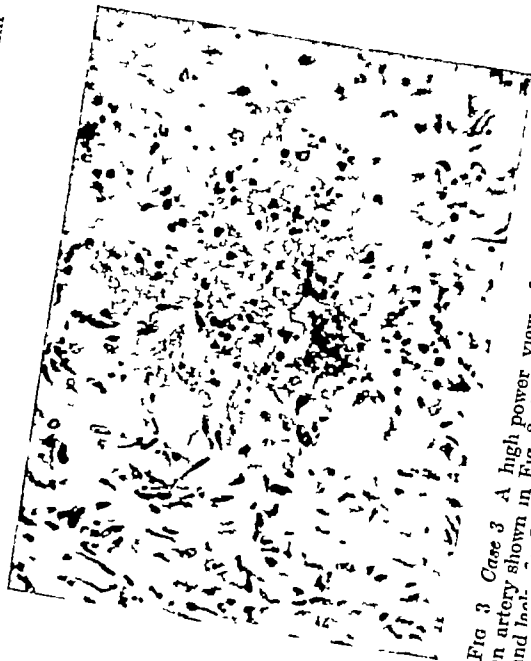


Fig 3 Case 3 A high power view of an area of necrosis in artery shown in Fig 2. Note the scanty cellular reaction and local inflammatory character ( $\times 270$ ) Stained haematoxylin and eosin

Fig 2 Case 3 Section of right temporal artery showing the inflammatory spread into the media and deeper layers of intima. Occasional areas of non-inflammatory necrosis are present. One of these is present in the media at the upper left margin of the figure ( $\times 50$ ) Stained haematoxylin and eosin



Fig 4 Case 3 Section of left temporal artery showing the pseudo follicular structures around the site of the original internal elastic lamina. New elastic fibres are appearing around these 'follicles' ( $\times 33$ ) Stained Weigert's elastica stain, counterstain carmalum







FIG 9 Case 3 Section of aorta showing the occasional extension of inflammation into the intima ( $\times 50$ ) Stained haematoxylin and eosin

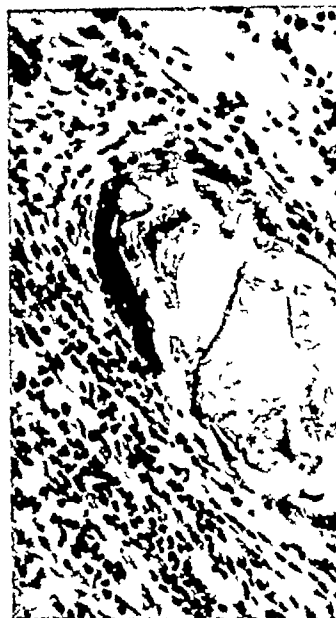


FIG 8 Case 3 Section of aorta showing the disruption of elastic tissue by the inflammation ( $\times 50$ ) Stained Voigt's elastic stain and carmalum





FIG 5 Case 3 High power view of part of left temporal artery showing an area of necrosis infiltrated by polymorphous plasma cells, and lymphocytes, in the situation of the internal elastic lamina (<250)

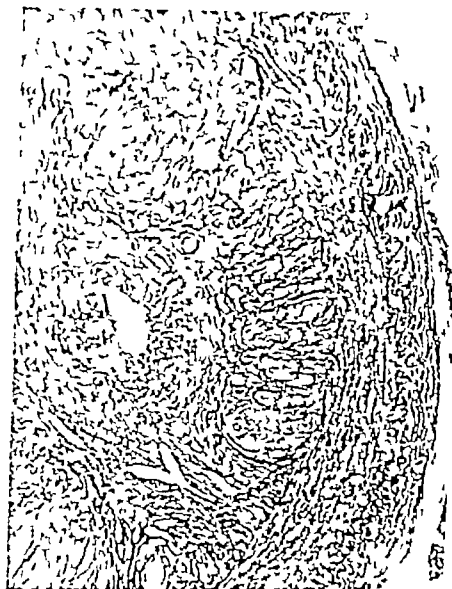


FIG 6 Case 3 The same artery stained by Foot's method to show the abundant formation of reticulum in the intima and around the site of the original elastica (<83)



FIG 7 Case 6 Section of retinal artery showing diffuse inflammatory change spreading from the adventitia through media. The lumen is obliterated by an organizing thrombus. The internal elastic lamina is calcified (<41) Stained haematoxylin and eosin



FIG. 16 Case 5. St.

ment and thickened  
branches



FIG. 17 Case 3 Heart and aorta showing sacular dilatation above aortic valve, rounded thrombus plaque on anterior wall of ascending arch, and "L" like thrombus on descending arch (marked).



FIG 12 Case 3 Section of right subclavian artery showing the marked reduplication of the elastic tissue. At one site the internal elastic lamina and part of the result of a mild lesion. The internal elastic lamina and part of the result of a mild lesion are replaced by a very vascular connective tissue of the media replaced by a very vascular connective tissue



FIG 13 Case 3 Section of kidney. Note the enlargement of the glomerular tuft, the thickening and hyalinization of the capillaries, and the adhesion between tuft and capsule. The surrounding tubules are very degenerate. Stained with hematoxylin and eosin



FIG 14 Case 4 Section of left temporal artery. Note the marked reduplication of the elastic tissue. At one site the internal elastic lamina and part of the result of a mild lesion are replaced by masses of closely packed pale cells. The lumen contains a thrombus, which was completely recanalized. Stained with hematoxylin and eosin



FIG 15 Case 4 Section of right temporal artery. Note the fragmentation of the internal elastic lamina and the production of granulation tissue between it and the media. Stained with hematoxylin and eosin



FIG 16 Case 5 Showing prominent and thickened temporal artery and branches



FIG 17 Case 3 Heart and aorta showing sacular dilatation above aortic valve, rounded thrombus plaque on anterior wall of ascending arch, and ribbon like thrombus on descending arch (marked by arrow)



# THE LEAD CONTENT OF THE BLOOD AND ITS RELATION TO RAREFYING PROCESSES IN BONE<sup>1</sup>

By ALEXANDER BROWN

(From the Royal Infirmary, Glasgow)

## *Introduction*

EVEN under the most primitive conditions lead has been found to be a natural constituent of the soil and vegetation, and lead occurs in the blood, urine, and faeces of human beings who subsist entirely on local agricultural and animal products (Kehoe, Thamann, and Cholak, 1933 *a*). Amid the more varied surroundings of civilization there is ample opportunity for the absorption of small amounts of lead, and the metal accumulates in the tissues until a state of equilibrium is reached (Kehoe, Thamann, and Cholak, 1933 *b*). Investigations on the lead content of normal foods by the same authors (1933 *c*) have shown clearly that a small quantity of the metal can be demonstrated in most foods commonly in use. In certain classes of food more than the average amount may be present owing to the methods of preparation and preservation employed. Drinking water may constitute a major source of lead if soft water flows through lead pipes or is allowed to stand in a lead tank. Even without these additional factors drinking water contains a demonstrable amount of lead. It is not surprising therefore that, whenever accurate methods of analysis have been applied to the various tissues of the body, lead has been detected in persons subject to no more than the normal domestic exposure. In a review on the lead hazard of the normal subject Minot (1938) concluded that the average daily incidental exposure is probably from 0.2 to 0.4 mg of lead. The results of Kehoe and his associates in the United States, and of Tompsett and Anderson (1935) in Glasgow are in close agreement in this respect. The latter authors investigated the lead content of the tissues obtained at autopsy from 20 persons with no known occupational exposure to lead. The metal was found in all the tissues examined. The mean concentrations in milligrams of lead per kilo of fresh tissue from adults were, liver 1.73, kidney 1.34, spleen 1.68, brain 0.5, rib 8.55, vertebra 7.09. Analysis of four foetuses (four to eight months gestation) revealed lower values, but again lead was found in all the tissues in each case. Examination of 25 samples of blood from 21 persons gave values of 40 to 70  $\mu\text{gm}$  per 100 c.c., with a mean value of 55  $\mu\text{gm}$ . It is evident that the highest concentrations of lead occur in the bones, a finding supported by all workers in this field. High concentrations may

<sup>1</sup> Received September 13, 1945



occur in the bones of older subjects (Minot, 1938) The femora and tibiae contain much higher concentrations than do ribs and vertebrae (Tompsett, 1936) The metal when ingested is first deposited in the trabeculae, and in time, as the less soluble tertiary phosphate, in the cortex (Gant, 1938) The more recently absorbed lead is thus stored in a situation from which it may be readily mobilized

In many respects the metabolism of lead and that of calcium are analogous Many factors influencing calcium storage and mobilization have been shown to affect lead in a like manner, but one aspect has been ignored Calcium may be mobilized by many osteolytic lesions and hypercalcaemia may follow It seems reasonable to suppose that, in a person even without occupational exposure to lead, the lead which is present in the bones may be mobilized by rarefying conditions affecting the skeleton The mobilization of calcium from the bones by conditions associated with local or general increase in bone-marrow activity is well known Hypercalcaemia has been recorded in myelomatosis (Baldridge and Fowler, 1933, Caylor and Nickel, 1933, North, 1936, Woodard and Higinbotham, 1937) and metastatic carcinoma (Mason and Warren, 1931, Baldridge and Fowler, 1933, Gutman, Tyson, and Gutman, 1936) Osteolytic bone lesions have been observed radiologically in lymphatic leukaemia (Poynton and Lightwood, 1932, Baldridge and Fowler, 1933, Snelling and Brown, 1934, Craver and Copeland, 1935, Clark, 1936, Connor, 1937) In other forms of leukaemia there is less tendency to demonstrable rarefaction of bone, but in one case of the myeloid type metastatic calcification occurred (Grayzel and Lederer, 1939) Even when there is no radiological evidence of bone absorption, the marrow hyperplasia of leukaemia or severe anaemia almost always produces trabecular absorption which can be demonstrated at autopsy The excretion of calcium is increased in hyperparathyroidism, and also in feeding with the thyroid hormone (Aub, Bauer, Heath, and Ropes, 1929, Blotner and Cutler, 1941) In these conditions calcium may be liberated from the skeleton, and hypercalcaemia result In these conditions also lead may be liberated and the lead content of the blood may be elevated above normal in persons not unduly exposed to the lead hazard

The observations which prompted the present investigation were related to a case described elsewhere (Brown and Tompsett, 1945) in which symptoms of lead poisoning developed suddenly at a time when no obvious explanation existed The man had been a type-setter for 12 years, when an acute generalized peripheral neuritis with flaccid paralysis developed without warning The most reasonable explanation was the liberation of stored lead in large amounts by marrow hyperplasia due to the development of subacute lymphatic leukaemia In this case, in a patient exposed to an abnormal lead hazard, the occurrence of marrow hyperplasia mobilized sufficient lead to cause acute symptoms of lead poisoning Death was due to acute plumbism rather than to the primary disease The chief purpose of the present study was to investigate how closely the lead-calcium analogy held good in relation to

rarefying processes involving the skeleton in subjects previously exposed only to the domestic lead hazard. The scope of the investigation and the methods are outlined below.

### *Clinical Material*

The subjects investigated comprised patients from the wards of the Glasgow Royal Infirmary, several from the wards of the Royal Cancer Hospital, and a number of senior medical students and colleagues. They can be grouped as follows:

Group	General description	Number of cases
I	Normal subjects or patients with anatomical defects	50
II	Patients with miscellaneous conditions	20
III	Patients with metabolic or endocrine abnormality	6
IV	Cases of carcinoma without radiological evidence of skeletal metastases	25
V	Cases of metastatic malignant disease demonstrable in bone	14
VI	Patients with undue activity of the reticulo endothelial system	26

### *Method of Estimation of Blood Lead*

Samples of venous blood were obtained by means of a dry, sterile, stainless steel needle and a clean dry all-glass syringe and collected into an acid-washed pyrex test-tube. The method employed was that of Tompsett (1939) by whom it has been described in detail. In extracting the diethyldithiocarbamate lead complex with ether, it has been found essential to avoid contamination of the extract with even minute amounts of the residue, because traces of copper carried into the final stages may inhibit completely the reaction between lead and dithizone. Throughout the estimations, and in the collection of blood samples, the greatest care was taken to ensure freedom from contamination with lead. The apparatus and reagents were prepared and used as described by Tompsett. In each estimation 18 to 20 c.c. of blood were used.

### *Results*

As a preliminary to a more detailed statement on the various types of case investigated, a summary of the results in the different groups is presented in Table I.

TABLE I  
*General Results*

Group	Number of cases	Blood lead in $\mu\text{gm}$ per 100 c.c. of blood										Mean
		10+	20+	30+	40+	50+	60+	70+	80+	90+	100+	
I	50	3	4	14	18	8	2	—	1	—	—	39.5
II	20	1	7	5	1	1	2	1	2	—	—	41.6
III	6	—	2	1	1	—	—	1	—	1	—	—
IV	25	7	5	1	4	3	—	—	3	—	2	—
V	14	—	—	1	1	1	—	—	1	4	6	91.5
VI	26	2	3	2	4	1	1	1	1	3	8	90.5*

\* Excluding four cases without marrow hyperplasia (Table VI, Part I).

*Group I Values in healthy adults* Blood-lead values were estimated in a series of normal subjects. The results form a base line to which the values

found in diseased patients may be referred. Altogether 50 normal subjects were investigated, comprising 22 medical students, six members of the hospital medical staff, and 22 patients attending hospital on account of some structural abnormality such as hernia, pes planus, or other local defect. Fourteen had been warded for one to three days before blood was withdrawn.

TABLE II  
*Miscellaneous Conditions*

Case No	Disease	Blood lead $\mu\text{gm}$ per 100 c c	Remarks
1	Chronic nephritis	37	Verified <i>post mortem</i>
2	Subacute nephritis	30	Nephrotic syndrome
3	Chronic nephritis	26	Blood urea 114 mg %
4	Essential hypertension	60	—
5	" "	20	—
6	" "	28	—
7	" "	27	—
8	Rheumatoid arthritis	75	—
9	" "	13	—
10	" "	24	—
11	" "	36	—
12	" "	85	—
13	Osteoarthritis	88	—
14	" "	63	—
15	Sciatica	39	Apparently primary
16	Spinal tuberculosis	33	Two vertebrae affected
17	Pyloric stenosis	23	Non malignant, little sickness
18	Senile osteoporosis	25	—
19	Paget's disease of bone	47	Phosphatase 16.8 units Calcium and phosphorus normal
20	" "	54	Phosphatase 21.0 units Calcium and phosphorus normal

The others were out-patients. The blood lead varied from 11 to 81  $\mu\text{gm}$  per 100 c c, with a mean of 39.5  $\mu\text{gm}$ , values in close agreement with the results obtained by other workers in Glasgow—Tompsett and Anderson (1935) 40 to 70  $\mu\text{gm}$  per 100 c c, and Chalmers (1940) 30 to 80  $\mu\text{gm}$  per 100 c c. They are of particular interest in relation to the values obtained in disease in patients from the same part of the country and therefore, in general, subject to roughly the same domestic lead hazard.

*Group II Values associated with miscellaneous diseases* Investigation of a group of cases of different types, unselected except that conditions associated with a high serum-calcium were excluded, was undertaken as an additional check on the values found in other groups. Twenty cases were investigated and the relevant details are described in Table II. The range of values obtained was from 13 to 88  $\mu\text{gm}$  per 100 c c, with a mean of 41.6  $\mu\text{gm}$ . These figures are not significantly different from the normal values.

*Group III Values in endocrine and metabolic disorders* Six cases of endocrine and metabolic disorders were investigated, comprising three cases of hyperthyroidism, two of myxoedema, and one of nutritional and lactation tetany, previously described by Anderson and Brown (1941). In all cases the results were within normal limits, but as may occur with many estimations,

it is impossible to be sure that a given value is a patient's normal level. The value may have altered significantly and still remain within the normal range. Case 22 is a case in point. A value of 98  $\mu\text{gm}$  per 100 c.c. was present before thyroidectomy and values of 57 to 38  $\mu\text{gm}$  one to six months after operation. Whether this represents a reduced mobilization of the metal

TABLE III  
*Endocrine and Metabolic Disorders*

Case No	Date	Disease	Blood-lead $\mu\text{gm}$ per 100 c.c.	Remarks
21	—	Hyperthyroidism	42	Before premedication
22	19 6 41	"	98	" "
	27 6 41	"	57	Four weeks after thyroidectomy
	15 12 41	"	38	Six months after thyroidectomy
23	23 12 41	"	70	B.M.R. + 75 %
	1 1 42	"	88	Untreated
	2 02 42	"	71	After operation
24	—	Myxoedema	26	—
25	22 1 42	"	26	No treatment
	2 2 42	"	33 and 42	" "
26	—	Low calcium tetany	30	Serum calcium 6.9 mg %

associated with a fall in the basal metabolic rate remains undecided, but the possibility must be admitted.

*Group IV Malignant disease without bone metastases* This group comprised 25 patients all of whom had a primary malignant tumour. In some the growth had been excised, and in some, whether or not local removal had been attempted, X-ray therapy was being given. In no case was there radiological evidence of skeletal metastases. The vertebral column, long bones, and pelvis were examined in all cases. In most instances only one lead estimation was carried out, but in a few the patient was re-examined at a later date and a further estimation performed. All but two patients showed values for blood lead within the normal range (Table IV). These two cases may have had secondary deposits in bone, but metastases were not demonstrable radiologically. Case 38, with a blood lead of 105  $\mu\text{gm}$  per 100 c.c., complained of pains in the limbs. Case 47, with a blood lead of 137  $\mu\text{gm}$  per 100 c.c., had no complaint, but subsequent examination revealed a blood lead of 122  $\mu\text{gm}$  and serum-calcium of 12.1 mg per 100 c.c. In six cases re-examined after an interval of one to five months the continued negative radiological findings were strong evidence that the previous normal lead value had been obtained in the absence of skeletal metastases.

*Group V Malignant disease with skeletal metastases* This group comprised 14 patients with secondary bone involvement by malignant disease. In nine the primary lesion was carcinoma of the breast. One case of sarcomatosis was included. All cases showed radiological evidence of bone involvement. The lead values and relevant clinical details are shown in Table V. A range of values from 36 to 140  $\mu\text{gm}$  per 100 c.c., with a mean of 91.5  $\mu\text{gm}$ , was observed. This represents a considerable extension of the range and a marked increase of the mean. It is of interest to note that in Case 62 at a second

TABLE IV

*Malignant Disease without Demonstrable Metastases in Bone*

Case No	Date	Primary lesion	Blood lead $\mu\text{gm}$ per 100 c c	Remarks
27	—	Carcinoma of breast	28	—
28	30 1 41	" "	54	—
	10 6 41	" "	54	Still feels very well
29	—	Carcinoma of larynx	25	—
30	—	Carcinoma of breast	16	—
31	—	Carcinoma of stomach	11	Metastases in liver
32	17 2 41	" "	16	No metastases
	5 3 41	" "	44	" "
	11 3 41	" "	70	" "
	30 4 41	" "	57	" "
33	—	Carcinoma of breast	20	—
34	—	Carcinoma of cervix	26	—
35	5 2 41	Carcinoma of breast	13	—
	7 7 41	" "	15	Oedema of arm
36	—	Spongiblastoma	16	—
37	—	" "	50	—
38	—	Carcinoma of cervix	105	Pains in limbs
39	—	Carcinoma of breast	15	—
40	—	" "	84	—
41	1 7 41	" "	40	—
42	—	" "	42	Glands involved
43	—	" "	10	Arm oedematous
44	2 10 41	" "	22	Skin involved
	22 1 42	" "	10	Still no bone metastases
45	7 11 41	" "	84	Glands involved
	15 12 41	" "	27	Still no bone metastases Calcium 10.6 mg %
46	—	" "	42	—
47	15 12 41	Carcinoma of prostate	137	No evidence of metastases
	18 12 41	" "	122	No evidence of metastases Calcium 12.1 mg %
48	9 10 41	Carcinoma of breast	37	—
	19 12 41	" "	46	No evidence of metastases
49	—	" "	45	—
50	—	Seminoma	56	Pain in back Calcium 10.2 mg %
51	24 12 41	Carcinoma of breast	82	Alive and well in 1943

TABLE V

*Malignant Disease with Metastases in Bone*

Case No	Date	Primary lesion	Blood lead $\mu\text{gm}$ per 100 c c	Remarks
52	—	Rib sarcoma	140	Skull, ribs, vertebrae, etc
53	—	Carcinoma of breast	94	Spinal metastases
54	—	" "	102	" "
55	—	Carcinoma of bronchus	124	Spine, long bones
56	—	Carcinoma of breast	98	" "
57	—	Carcinoma of bronchus	99	Cervical vertebra
58	—	Carcinoma of breast	98	Spine, long bones
59	—	" "	103	" "
60	—	Malignant melanoma	36	Spine
61	—	Carcinoma of prostate	57	Pelvis (osteoplastic)
62	10 12 41	Carcinoma of breast	113	In head of humerus
	18 12 41	" "	60	Serum calcium 12.0 mg %
63	—	" "	82	Direct invasion of sternum
64	—	" "	118	Spine, pelvis
65	—	" "	47	Clavicle Serum calcium 13.2 mg %

examination the blood lead had fallen to normal, but the serum-calcium was 12.0 mg per 100 c.c. In Case 65 a normal blood lead was found in association with hypercalcaemia

TABLE VI

*Diseases of the Reticulo-Endothelial System*Part I *Cases Without Marrow Hyperplasia*

Case No	Condition	Blood lead $\mu\text{gm}$ per 100 c.c.	Remarks
66	Pernicious anaemia	36	Under control
67	" "	88	" "
68	" "	46 and 56	Almost complete aplasia
	—	33	Post-mortem specimen
69	Lymphadenoma*	23	Not anaemic, normal marrow

\* X-ray therapy for next four months, range of values in five estimations 10 to 45  $\mu\text{gm}$  per 100 c.c.

Part II *Cases With Marrow Hyperplasia*

Case No	Date	Condition	Blood lead $\mu\text{gm}$ per 100 c.c.	Remarks
70	—	Chronic myeloid leukaemia	146	Untreated
71	—	" " "	125	"
72	7 2 41	" " "	95	"
73	24 6 41	" " "	109	"
74	3 11 41	" " "	27	Untreated Calcium 9.6 mg %
	8 12 41	—	30	Treated Calcium 11.0 mg %
75	—	Acute myeloid leukaemia	246	Untreated
76	—	" " "	50	"
77	—	" " "	25	"
78	—	" " "	92	"
79	—	" " "	75	"
80	—	Chronic lymphatic leukaemia	13	Treated
81	—	Subacute lymphatic leukaemia	101	Untreated
82	19 9 41	Plasma cell multiple myeloma*	130	"
83	23 4 41	Pernicious anaemia	266 and 240	"
84	9 7 41	" "	93	"
85	24 12 41	" "	40 and 37	"
86	31 12 41	" "	40	"
87	—	" "	63	"
88	11 4 41	Iron deficiency	105	"
	17 4 41	" "	104	Treated
	24 4 41	" "	80	—
89	10 7 41	" "	46	Untreated
	16 10 41	" "	42	Recovered
90	18 2 41	Syphilis and anaemia†	16	Untreated
			No change	
91	22 12 41	Haematemesi	48	Reticulocytes 9 %
	24 12 41	—	85	" 10 %

\* During next three months, four values 41 to 62  $\mu\text{gm}$  per 100 c.c.

† At intervals of three to seven days for four weeks, no significant change

*Group VI Diseases of the reticulo-endothelial system* This group comprised 26 patients who had some abnormality of the reticulo-endothelial system. In some no marrow hyperplasia was expected because there was no evidence of medullary involvement by disease, and the peripheral blood was normal. In others the nature of the disease and marrow examination indicated undue

marrow activity The results and relevant details are shown in Table VI In Part I of Table VI are four cases in which no undue marrow activity was found or expected. Cases 66 and 67 were practically normal subjects Case 68 was a severe case of pernicious anaemia with subacute combined degeneration of the spinal cord He died of the latter condition, and at

TABLE VII  
*Effect of X-ray Therapy in Leukaemia*

CASE NO 72

Date (1941)	White cells per c mm	Blood lead $\mu\text{gm}$ per 100 c c
February 7	430,000	95
" 10*	—	95
" 13	200,000	31
" 15	150,000	21
" 18	105,000	23
" 21	98,000	39
" 26	105,000	107
March 3	38,000	15
June 11	18,000	45
October 1	—	82
" 16	—	54
" 23	—	90
December 18	—	36 and 41†

\* Therapy began February 10, 15 minutes before blood withdrawn

† Serum-calcium 12.1 mg %.

CASE NO 73

Date (1941)	White cells per c mm	Blood lead $\mu\text{gm}$ per 100 c c
June 24	140,000	109
" 28	—	68
July 2*	—	43
" 3	160,000	36
" 4	186,000	26
" 5	—	134
" 7	176,000	24
" 9	170,000	80
" 10	—	43
" 11	—	31
" 16	190,000	45
" 19	180,000	51
" 23	—	10

\* Therapy begun four hours before blood withdrawn

autopsy active bone-marrow was found to be confined to a very small area of the upper end of the manubrium sterni Case 69 was observed over two years, during which time the peripheral blood remained normal Lead values on five occasions ranged from 10 to 45  $\mu\text{gm}$  per 100 c c Examination of the bone-marrow on three occasions revealed nothing abnormal, and there was no radiological evidence of bone absorption In Part II of Table VI are summarized the findings in 22 cases in which undue marrow activity was present Only two of five cases of chronic myeloid leukaemia showed a value for blood lead within normal limits In one (Case 72) the value was at the

TABLE VIII

*Effect of Specific Therapy in Pernicious Anaemia*

## CASE No 83

Date (1941)	Red cells, millions per c mm	Blood lead $\mu$ gm per 100 c c
April 23	1 50	266
May 6	1 50	186
" 9*	1 40	148
" 12	1 74	100
" 15†	2 00	40
" 18	2 40	83
" 21	3 00	56
" 24	3 25	30
June 2	4 27	71
" 13	4 46	56

\* Liver therapy begun

† Reticulocyte response maximal

## CASE No 84

Date (1941)	Red cells, millions per c mm	Blood lead $\mu$ gm per 100 c c
July 9*	1 55	93
" 10	—	19
" 11	1 53	15
" 13	1 53	—
" 14†	—	20
" 15	1 77	—
" 16	—	14
" 19	1 98	57
" 21	2 10	—
" 22	—	35

\* Liver therapy begun

† Reticulocyte response maximal

## CASE No 85

Date (1941-2)	Blood lead $\mu$ gm per 100 c c
December 24	40 and 37
" 26	51
January 12*	25
" 17	66
" 21	27
" 24	26
" 30	56
February 5	68

\* Liver therapy begun.

## CASE No 86

Date (1941-2)	Blood lead $\mu$ gm per 100 c c
December 31	40
January 2	45
" 5*	40
" 9	48
" 15	25
" 18	37
" 21	34
" 24	28

\* Liver therapy begun



upper limit of normal and fell with X-ray therapy (Table VII). In five cases of acute myeloid leukaemia one showed a very high lead value, and one showed a value at the upper limit of normal. One case of untreated subacute lymphatic leukaemia showed a high value. In repeated examinations of a case of plasma-cell myelomatosis showing osteolytic lesions throughout the skeleton an initial value of 130  $\mu\text{gm}$  per 100 cc was found. Subsequent values were within normal limits. In five cases of untreated pernicious anaemia a high blood level was found in one. In Case 84 a high normal level fell with treatment. Serial estimations revealed no significant change in blood-lead level in two cases. One case of iron deficiency anaemia showed a high value which fell with iron therapy. A second case showed no significant variation before and after treatment. In Case 90, with anaemia and a hyperplastic marrow in association with syphilis, no abnormal lead levels were found on repeated examination. In Case 91 a rise in blood lead was observed during the reaction to a severe haematemesis.

*Further observations on the effect of treatment on lead levels in leukaemia and pernicious anaemia.* Serial estimations of blood lead were made in two cases of chronic myeloid leukaemia. The results and relevant details are shown in Table VII. In Case 72 the initial values were high, but not abnormally so, but immediately after X-ray treatment lower values obtained for about 10 days. A sudden rise in lead occurred during treatment and thereafter low values were found. In this case the lead values were more or less parallel to the white cell count. In Case 73, although an initial high level was observed, considerable fluctuation occurred before X-ray therapy was instituted. On the whole, however, lower values obtained with treatment, although the white-cell count was not significantly affected. Serial lead estimations were carried out in four cases of pernicious anaemia. In each case diagnosis was established on blood and bone-marrow findings. A histamine-fast achlorhydria was present in all. In all the initial red-cell count was below 1,500,000 per cmm and counts over 4,000,000 per cmm were established within 40 days of commencing treatment with liver. In two cases treatment was followed by a reduction in blood-lead levels (Table VIII). The original level in one was distinctly abnormal, while in the second, a value of 93  $\mu\text{gm}$  was obtained. In the two cases in which initial values were on the low side of normal no significant change in the blood lead was observed to follow treatment.

### Discussion

Investigation of the common foods has revealed a general source of small amounts of lead. Certain classes of foods may contain more than average amounts, for example, bread, meats, tinned foods, and green vegetables (Kehoe, Thamann, and Cholak, 1933c). In certain circumstances the water-supply may constitute a very real addition to the domestic hazard. The majority of town dwellings are not new, lead pipes are common, and storage tanks are often lead-lined. Specially when the water is soft, stagnation over-

night may result in the passage into solution of appreciable amounts of lead. Considerable variation in the lead content of the water-supplies may therefore be expected, and the figures for several Glasgow districts demonstrate this (Table IX). There is some doubt of the daily intake which should be regarded as dangerous, but it is evident that many people in Glasgow are

TABLE IX  
*The Domestic Water-supply*

District	Description of supply	Lead in mg per litre	
1	Glasgow Royal Infirmary	0 03	
2	Water drawn from large lead storage tank	Morning	0 49
		Mid-day	0 54
		4 p m	0 55
		Evening	0 34
3	Tenement with lead inlet pipe	0 09	
4	Water drawn from large lead storage tank	0 27	
5	Morning sample from supply of Case 83	0 31	

exposed to a considerable domestic hazard. In some houses from this source alone a daily intake of as much as 1 mg of lead may be anticipated. Whether or not this high level is reached, the average individual is undoubtedly exposed to small amounts of lead, and the metal is stored in most of the body tissues. The highest concentration occurs in the skeleton, particularly in the femur and tibia (Lynch, Slater, and Osler, 1934, Tompsett and Anderson, 1935, Tompsett, 1936). Deposition of lead in the bones occurs most rapidly in the growing animal (Shields, Mitchell, and Ruth, 1940). Recently absorbed lead is stored in the trabeculae and in time it is deposited in the cortex as the less soluble tertiary phosphate (Gant, 1938). The trabeculae tend to contain higher concentrations than do the corticals (Aub, Robb, and Rossmesl, 1932).

In proportion to the magnitude and rapidity of the osteolytic process, metastatic carcinoma and other rarefying bone lesions may be expected to liberate lead from the skeleton. The amount of lead liberated will depend on recent exposure to lead, because in all cases trabecular absorption is the first change to occur. In cases with slight exposure the most active rarefying bone lesions may cause little or no increase in the blood lead, which remains low throughout. In cases with an unusually severe domestic exposure the occasional occurrence of high blood values is to be expected, specially early in the disease and in its most active phase. An occasional report in the literature on lead metabolism contains matter of interest in this respect. Reference has already been made to the case of lead poisoning occurring in a lead worker in association with, and probably precipitated by, subacute lymphatic leukaemia (Brown and Tompsett, 1945). Gant (1938) described the case of a man aged 43 years who had worked with lead for 13 years. He died of sarcomatosis and lead poisoning. The possibility of mobilization of lead from the skeleton by the disease was not considered. Case 35 in the same series was a woman of 40 years who was given 300 mg lead, as the

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It may be that factors other than treatment played a part in reducing the blood lead in these cases. Admission to hospital, and the change from a high domestic lead hazard to one which was very small (Table IX), may have been significant in this respect. Thus lead is a normal hazard. An additional intake may occur in various circumstances some of which are certainly domestic. The bones of the average person contain a significant amount of lead, some of which may be mobilized by any osteolytic process. The occurrence of rarefying disease in bone may be associated with blood levels considerably above normal, and this response will be accentuated in proportion to the domestic hazard. In circumstances associated with chronic exposure to lead in great degree, such as may occur in industry, the occurrence of rarefying processes in bone may precipitate lead poisoning. The blood-lead level is an index not of recent lead absorption alone, but of the balance struck between lead absorption and mobilization, and its excretion. A patient may be anaemic because of lead intoxication, he may be suffering from lead intoxication because he is anaemic, or because for some other reason his marrow is unusually active.

### *Summary*

1 In an investigation on 50 healthy adults, the lead content of the blood was found to be 11 to 81  $\mu\text{gm}$  per 100 c.c. Only one subject showed a blood level over 70  $\mu\text{gm}$ .

2 In a series of 91 patients with various diseases 24 showed a blood lead of over 90  $\mu\text{gm}$  per 100 c.c. In all but two of these there was evidence of undue marrow activity, secondary involvement of the skeleton by malignant disease, or hypercalcaemia.

3 The highest values in the series were obtained from a case of pernicious anaemia (266  $\mu\text{gm}$  per 100 c.c.) and from one of myeloid leukaemia (246  $\mu\text{gm}$  per 100 c.c.) In the former the domestic hazard was found to be unusually great on account of the high lead content of the domestic water-supply (0.31 mg. per litre).

4 High blood-lead concentrations may result from rarefying processes in bone, even in persons without industrial exposure.

5 High concentrations of lead in the blood may not signify direct exogenous intoxication.

My thanks are due to the members of the Staff of the Royal Infirmary and the Royal Cancer Hospital, Glasgow, for permission to investigate patients under their care, to Professor J. W. S. Blacklock for permission to undertake the work from the Department of Pathology at the Royal Infirmary, and to Dr. A. B. Anderson for helpful criticism and advice. Dr. S. L. Tompsett kindly supplied the values quoted in Table IX, districts 1 to 4.

Part of the expenses of this work was defrayed by a grant from the Rankin Fund of the University of Glasgow.

colloidal phosphate, over 15 days for recurrent breast carcinoma with generalized metastases. Death occurred four weeks later, although the preparation is reported to be of relatively low toxicity. There was much greater retention of lead in the kidney (2.52 mg per cent) than has been found in other cases treated in a similar way. Gant ascribed the deficient storage in the bones to the time factor, but it may be that storage was deficient owing to the multiple skeletal metastases. In a review of the blood-lead values of 189 cases, none of which had had abnormal exposure to lead, Willoughby and Wilkins (1938) included 145 cases with carcinoma and eight with myeloid leukaemia. The blood-lead value in the whole series ranged from 0.00 to 0.09 mg per 100 c.c. Only nine cases showed a value above 0.06 mg per 100 c.c. and all these were in the 'malignant' class. No details as to the presence or absence of metastases in the cases of carcinoma were given, and the authors concluded that the malignant and non-malignant groups were in agreement.

In the present review of 141 subjects 50 were healthy and 20 comprised a group of miscellaneous conditions in which a raised serum-calcium was highly improbable. The range of values from each group was not significantly different—10 to 88  $\mu$ gm per 100 c.c. The great majority of cases of malignant disease without X-ray evidence of bone involvement showed values within this range. In two cases, however, raised values were obtained, but in them the possibility of the presence of metastases could not be excluded. Skeletal metastases may be massive and widespread before they are visible radiologically (Wolfson, Reznick, and Gunther, 1941). Almost the entire spongiosa of a vertebral body may be replaced by metastatic tumour without alteration in the X-ray appearances (Snure and Maner, 1937). In the first case (No. 38) the symptoms were in keeping with bone deposits. Although the second case was free from symptoms, the primary growth was of the type which commonly spreads to bone. In addition hypercalcaemia was present. Of 14 cases of malignant disease showing skeletal involvement, 10 showed blood-lead values above 90  $\mu$ gm per 100 c.c. Two cases showed normal lead values in the presence of hypercalcaemia. Of four cases of reticulo-endothelial disease without evident marrow hyperplasia at the time of examination, none showed a high blood lead, but among the cases with obvious marrow hyperplasia high values were frequently encountered. It is of special interest that the hyperplasia in severe anaemia may be associated with increased blood levels. In Case 83, in which initial levels were abnormal, the domestic hazard was undoubtedly above normal (Table IX). In both anaemia and leukaemia the effect of reduction in marrow activity has been to reduce the blood-lead levels. In leukaemia, particularly, the levels are unstable. This may be related to the availability of the recently stored lead. With X-ray therapy and reduced marrow activity lead will be stored in the trabecular bone, whence it may be rapidly mobilized with the slightest increase in marrow activity. The lead levels cannot be predicted from consideration of the white-cell count (Case 73, Table VII).

# DESCRIPTION OF AN OUTBREAK OF BERIBERI<sup>1</sup> WITH SPECIAL REFERENCE TO THE AETIOLOGY OF BERIBERI AND EPIDEMIC DROPSY

By E R CULLINAN, A KEKWICK, AND A S WATTS  
(from East Africa Command) AND W L TITMAN (Medical  
Department, Kenya Colony)

With Plate 6

## *Introduction*

THE various forms of the clinical syndrome which has become known as beriberi have been recognized for many years. The neuritis was described in 1642, while the wet form was associated with it in 1835 (Bicknell and Prescott, 1942). The classical observations of Takaki (1887), Eijkman (1897), and many other later workers led to the conception that the cause of the condition is a lack of thiamin in the diet. Epidemics of the disease, however, have been described among people whose thiamin intake has been theoretically sufficient for health, and most clinical observers consider that thiamin lack alone is an over-simplification, and that in outbreaks of beriberi other aetiological factors are present (Williams, Mason, Wilder, and Smith, 1940, Meiklejohn, 1940, Walshe, 1941). By some it has been thought that, because thiamin is intimately bound up with carbohydrate metabolism, the amount of thiamin in relation to the calorie value of the diet is the all-important factor (Williams and Mason, 1941, Cowgill, 1938). More recently, in India epidemics of dropsy, clinically almost indistinguishable from the wet form of beriberi, have been attributed to a toxic factor either in rice or in other food in the diet (Bigland, 1934, Mukherji, Lal, and Mathur, 1941). There exists therefore amongst populations whose staple food is rice a clinical pattern for which aetiological factors have been found, some known and some only surmised. Of those known lack of thiamin producing beriberi, and a toxin producing epidemic dropsy are the most important. The present paper is a report of an outbreak of the syndrome amongst troops where it was possible to trace in detail the sources and issues of the various articles of their food. A detailed study was made of the epidemic with a view to collecting evidence which might throw light on the aetiological factors involved in the production of the syndrome.

## *The Outbreak*

The troops were part of the East African forces, and were located in an isolated island garrison town which had irregular communication with the

<sup>1</sup> Received September 20, 1945

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mainland by ship and some communication by aircraft. They were made up of three races, British, African, and Mauritian. The local situations were such that the central small garrison town housed a number of units, all of which were comparatively small in number (Table VIII, Group A). Apart from these troops there were two outlying sections of the garrison several miles distant, each communicating with the garrison town by a road (Table VIII, Group B and C). All troops were housed in good barracks and were living in excellent conditions. The climate of the area was hot and humid, but the climatic conditions during the time of the outbreak were not different from those at similar times during previous years. Suddenly on March 12, 1945, nine men from Group B reported sick to their medical officer with oedema of the legs. The medical officer carried out an inspection of all the remaining troops in the group, and a further 26 men were found to be affected. During the subsequent few days (up to March 22) the whole garrison of 1,546 Mauritians and Africans were examined and all Europeans questioned. A further 24 cases were found, making a total of 59 cases, an incidence of 38 per 1,000. All these cases occurred in native troops recruited from the East African territories, no Europeans and no Mauritians were found to have oedema of the legs.

From the subsequent sections it will be seen that we considered that the rice diet of the garrison was at fault, and on March 24 the diet was altered. From this time onwards the number of cases steadily diminished, and finally, a week later, on April 1, 1945, no further cases were being reported, the outbreak had ceased as suddenly as it had begun.

### *The Syndrome*

Twenty-two cases were carefully examined in hospital (Table I). The patients had been ill for an average time of 11 days. The range, except for one patient, who stated that he had been ill for 30 days, was three to 20 days. Excluding the exception, the onset of the outbreak must have been about February 27, 1945.

All the patients complained of an initial swelling of the legs, in many this was followed by a feeling of tightness of the legs on walking, and in some of pain. Many complained of weakness of the legs and a few of general fatigue. In two cases the gait was markedly affected. All patients were apyrexial while in hospital. The general physical state was, if anything, better than in a large group of East African native soldiers examined during a nutritional survey on the standard army diet (Kekwick and Wright). Other monosymptomatic evidence of malnutrition was consistently absent. In only two patients could mosaic skin or abnormal pigmentation of the tongue be found. Pitting oedema extended up to the knees in all (Plate 6, Fig 1). Evidence of venous or lymphatic obstruction was sought, as these two conditions, produced on the one hand by thrombophlebitis and on the other by buboes, are not uncommon amongst such troops. No evidence of either could be found.



TABLE I

## Clinical Table

Case No	General nutrition	Oedema	Peripheral neuritis	Pulse rate	Blood-pressure	Sedimentation rate at 15 min (corrected) intervals	Adrenalin test (diastolic pressure)	White cells per c mm	X-ray of heart	Electrocardiogram	Tyrene-tolerance test	Hæmatocrit	Capillary fragility	Urine
1	Good	+	+	62	100/100	12.57	100 105 100	7100	RSD	RVP SPR	N	45	1	Alb + Chloride +
2	"	+	+	62	135/85	0 0 2	85 90 85	3400	—	SPR	N	40	0	0
3	"	+	+	72	125/85	0 0 7	85 90 80	3000	—	—	N	38	0	0
4	"	+	+	64	140/90	0 1 2	90 85 85	4200	RSD	RVP	N	43	0	0
5	"	+	+	68	100/85	0 0 1	85 90 90	2400	Normal	SPR	N	34	0	0
6	"	+	+	68	125/65	0 19 24.40	65 65 65	—	—	Normal RVP	N	33	0	0
7	"	+	0	76	115/60	0 1 2 4	60 50 60	—	—	Normal	N	45	0	0
8	"	+	+	60	120/65	0 1 2 3	65 60 70	—	RSD	—	N	42	0	0
9	Fair	+	+	72	150/65	0 5 9	65 60 65	—	Normal	—	N	34	0	0
10	Good	+	+	84	140/85	0 1 3 4	85 90 80	2800	"	—	Slightly impaired	14	3	0
11	"	+	+	60	110/75	0 2 16	75 75 70	4800	—	—	"	42	0	0
12	Fair	+	+	76	120/65	0 3 7	65 70 65	4000	—	—	"	41	1	0
13	Good	+	+	86	140/85	0 3 7	85 85 85	6000	—	—	N	35	0	0
14	"	+	+	76	140/95	0 1 2 4	95 100 100	4600	—	—	N	41	0	0
15	"	+	+	84	120/85	0 2 4	85 85 80	5100	—	—	N	39	0	0
16	"	+	+	88	160/85	0 5 7	85 80 80	5800	—	—	N	34	0	0
17	"	+	+	78	145/85	0 3 7 16	85 100 90	3000	—	—	Slightly impaired	42	0	0
18	"	+	+	68	140/90	0 1 3 4	60 50 55	3600	—	—	"	46	1	+
19	"	+	+	100	150/90	0 3 6	90 85 85	9000	RSD	SPR RVP	N	37	0	0
20	"	+	+	76	160/80	0 3 6	80 80 80	5800	—	—	N	35	0	0
21	"	+	+	68	120/75	Not done	75 65 75	—	—	—	Slightly impaired	—	0	0
22	"	+	+	64	140/90	0 0 1	90 100 90	3800	Normal	SPR	N	36	2	0

Note —SPR = Shortening of P/R interval below 0.14 sec RVP = Right ventricular preponderance RSD = Right-sided dilatation

mainland by ship and some communication by aircraft. They were made up of three races, British, African, and Mauritian. The local situations were such that the central small garrison town housed a number of units, all of which were comparatively small in number (Table VIII, Group A). Apart from these troops there were two outlying sections of the garrison several miles distant, each communicating with the garrison town by a road (Table VIII, Group B and C). All troops were housed in good barracks and were living in excellent conditions. The climate of the area was hot and humid, but the climatic conditions during the time of the outbreak were not different from those at similar times during previous years. Suddenly on March 12, 1945, nine men from Group B reported sick to their medical officer with oedema of the legs. The medical officer carried out an inspection of all the remaining troops in the group, and a further 26 men were found to be affected. During the subsequent few days (up to March 22) the whole garrison of 1,546 Mauritians and Africans were examined and all Europeans questioned. A further 24 cases were found, making a total of 59 cases, an incidence of 38 per 1,000. All these cases occurred in native troops recruited from the East African territories, no Europeans and no Mauritians were found to have oedema of the legs.

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Peripheral neuritis was evidenced by sluggish or absent deep reflexes in 18 cases, and diminution of sensation to light touch or superficial pain in 16 cases. Deep sensation was unaffected. Nothing else abnormal was found on examination of the nervous system. There were no abnormal signs in the lungs or abdomen. The pulse-rates were high in five of the men (88 to 100), and normal in 17. The systolic and diastolic blood-pressure were normal. The exercise tolerance tests were slightly abnormal in seven. No clinical evidence of enlargement of the heart was discovered, but telerradiograms revealed right-sided dilatation of the heart in four out of eight, and the size was at the upper limit of normal in a further two. Electrocardiograph records were taken of nine patients. Right ventricular preponderance was shown in three, shortening of the P/R interval was present in almost all cases and was below 0.14 sec. in five. The adrenalin test was made in all cases. This test consists of measuring the effect of adrenalin on the blood-pressure. It is said that in beriberi the diastolic pressure drops sharply (Bicknell and Prescott, 1942). In all 22 cases the response was normal and no significant drop could be obtained. Urines were examined and all found to contain chlorides, giving evidence that chloride metabolism was intact. One urine contained albumin. The white-cell counts and differential counts were normal in all. The sedimentation rate was raised in two and normal in 19 cases. The capillary fragility test was normal in all. The packed-cell volume of the red blood corpuscles was estimated and found to be low in 11 of the 22 cases. One of the most interesting features was the plasma-proteins. From a study of normal East African native soldiers it had been previously found (Kekwick and Wright) that on the standard army diet the total protein figures were within the normal range for Europeans, but the albumin globulin ratio was significantly reduced. The mean figures and standard deviations were

Total protein	7.15 $\pm$ 0.6
Albumin	3.01 $\pm$ 0.46
Globulin	3.24 $\pm$ 0.56
Albumin globulin ratio	1.22 $\pm$ 0.26

It can be seen (Table II) that in the patients with oedema the total protein figures were within the normal European range, but the albumin globulin ratio was raised rather than lowered. We were unable to account for this finding.

After this 63 cases were treated under controlled conditions. They were divided into three groups, in the first the patients were given 1 mg. of thiamin and 1 oz. of yeast daily, in the second 1 oz. of yeast, and in the third a small dose of ammonium chloride as a control. Table III shows the details of recovery of the three groups. It will be noticed, comparing Groups 1 and 3, that the time between the start of the disease and the start of treatment was comparable, but that the duration of the disease had been shortened in Group 1. Group 2 occupies an intermediate position.

It appears that the oedema of the legs which was the presenting sign in

these cases, was caused neither by venous or lymphatic obstruction, hypoproteinaemia, or renal disease. The right-sided dilatation of the heart and the peripheral neuritis support our opinion that this was indeed an outbreak of a beriberi-like syndrome. Furthermore, it appears that the administration of thiamin exerted a beneficial effect on the course of the disease. As regards the clinical differentiation between the two diseases

TABLE II  
*Plasma-Protein Estimations on 12 Cases*

Case No	Total protein (gm per 100 c c)	Albumin (gm per 100 c c)	Globulin (gm per 100 c c)	Albumin globulin ratio
1	7.56	5.26	2.30	2.3 1
2	7.14	4.99	2.15	2.3 1
3	8.55	5.40	3.15	1.7 1
4	8.34	5.40	2.94	1.8 1
5	6.84	5.40	1.44	3.7 1
6	6.75	4.32	2.43	1.8 1
7	7.50	4.78	2.72	1.7 1
8	7.20	5.33	1.87	2.8 1
9	6.98	4.99	1.97	2.5 1
16	7.44	4.99	2.45	2.0 1
19	7.95	5.40	2.55	2.1 1
22	6.36	4.80	1.56	3.1 1

TABLE III  
*Results of Treatment*

	Number of patients	Illness to start of treatment (mean days)	Duration of treatment (mean days)	Total duration of illness (mean days)
Group 1 (1 oz. yeast and 1 mg thiamin daily)	29	2.45 (0 to 13)	6.4 (1 to 18)	8.9 (1 to 19)
Group 2 (1 oz. yeast daily)	18	0.833 (0 to 2)	9.22 (1 to 17)	10.55 (3 to 18)
Group 3 Ammonium chloride (as a control)	16	3.31 (1 to 10)	12.0 (1 to 21)	14.7 (4 to 27)

Note.—Figures in brackets indicate limits in number of days

beriberi and epidemic dropsy, in favour of beriberi are firstly the absence of haemorrhages and the normal capillary fragility (Lal and Roy, 1937) and secondly the absence of any marked gastro-intestinal symptoms (Bigland, 1934). In favour of epidemic dropsy are the facts firstly, that muscle tenderness was absent, secondly, that the haematocrit readings were low, and thirdly, that the signs of peripheral neuritis when present were of such a mild character that they might have been produced only by the oedema acting on suggestible subjects.

#### *The Diet*

The standard diet of East African native troops has been described elsewhere (Anderson, 1943) and is shown in Table IV. The diet is not very

varied in relation to the foodstuffs issued and does not contain a very high proportion of first-class protein. From the point of view of the present paper the important factor is that the staple article of food in the diet was maize meal, a food which also provides the largest proportion of the diets of these natives in their homes. In November 1944 it was found that the isolated position of the garrison and the fact that maize meal did not keep well

TABLE IV  
*Standard Daily Ration Scale, African Troops*

Commodity	Quantity issued, oz. (approximate)
Maize meal	16
Rice, milled, raw	4
Meat, fresh, low grade	8
Ghee or substitute	1
Fresh vegetables	4
Potatoes or	6
Sweet potatoes or	6
Peas or	4
Beans or	4
Groundnuts or	4
Choroko (peas)	3
Orange	3
Sugar	2
Salt	$\frac{1}{2}$
Ten	$\frac{1}{4}$

under the climatic conditions precluded the use of maize meal as the staple food in the diet. Nineteen ounces of rice were therefore substituted for the previous issues of 16 oz. of maize meal and 4 oz. of rice. In February 1945 the stock of beans in the garrison was condemned owing to high weevil infestation. Further, during the months of January and February fresh vegetables were in short supply. By the middle of February the diet of the African native troops was considerably changed and from this time onwards was as shown in Table V. The European and Mauritian troops were on different scales and these are represented in Tables VI and VII. It can be seen by comparison of Tables V, VI, and VII that the main differences between the food of the three races concerned were as follows. Firstly, the diet of the Mauritians and Europeans was considerably more varied than that of the Africans, secondly, rice formed a much greater proportion of the African diet both in relation to known food factors and to bulk, and thirdly, the relation of first to second class protein was better in the European and Mauritian diets. All three diets were theoretically adequate in known food factors. The sources of all foodstuffs were common to all three races, as they were issued to the various units from a central pool.

Attention was concentrated on the rice supply for obvious reasons. The rice was stored under good conditions in sacks. It was, however, old, and indeed no information could be obtained as to when it had been cropped. On inspection it appeared to be lightly milled, and this was later confirmed by tests of uncooked rice which was found to contain 0.03 mg. of thiamin per oz. (mean figure of 15 samples). Mycological examination showed

*Daily Ration Scale, African Troops, February, 1945*

	Quantity issued (oz approximate)	Protein (gm)	Fat (gm)	Carbo- hydrate (gm)	Calcium (mg)	Iron (mg)	Vita- min A (i u)	Vita- min B1 (mg)	Ribo- flavin (mg)	Nicotinic acid (mg)	Vita- min C (mg)	Calories
Rice	10	34	6	422	19	1.9	—	0.61*	0.38	5.7	—	1881
Meat, fresh, low- grade, native	8	39	36	—	24	8.8	112	0.17	0.56	10.4	—	480
Ghee	1	—	26	—	—	—	590	—	—	—	—	228
Fresh vegetables	2	—	—	—	24	0.2	60	0.12	0.02	—	22	4
Fresh fruit	2	6	—	6	30	0.4	46	0.03	—	0.8	32	26
Sugar	2	—	—	52	—	—	—	—	—	—	—	216
Totals	34	70	68	480	97	11.3	808	0.93	0.96	16.9	54.0	2835

\* Direct estimation

Note —The above food values, and those in Tables VI and VII, have been estimated from 'Nutritive Value of Foodstuffs',  
The War Office, March, 1945

TABLE VI

*Daily Ration Scale, European Troops*

	Quantity issued (oz approximate)	Protein (gm)	Fat (gm)	Carbo- hydrate (gm)	Calcium (mg)	Iron (mg)	Vita- min A (i u)	Vita- min B1 (mg)	Ribo- flavin (mg)	Nicotinic acid (mg)	Vita- min C (mg)	Calories
Bread, white, 70% extraction	12	28*	2	187	48.0	2.4	—	0.18	0.12	2.4	—	876
Meat, low grade	12	58	54	—	36.0	13.2	168	0.25	0.84	15.6	—	720
Butter	4	—	18	—	3.0	—	855	—	—	—	—	168
Bacon or sausage	2	6	25	—	6.0	0.6	—	0.20	0.12	0.6	—	190
Cooking fat (lard)	1	—	28	—	—	—	—	—	—	—	—	253
Milk, condensed, evaporated, unsweetened	2½	5	6	7	172.5	0.3	225	0.04	0.25	0.3	—	100
Fresh fruit	4	1	—	12	60.0	—	92	0.05	—	1.6	64.0	52
Fresh vegetables	4	1	—	1	48.0	0.4	120	0.24	0.04	—	44.0	8
Sugar	4	—	—	104	—	—	—	—	—	—	—	432
Potatoes	4	2	—	18	8.0	0.8	—	0.13	0.08	1.2	8.0	84
Jam	½	—	—	4	0.8	0.1	1	—	—	—	0.8	18
Totals	—	101	133	333	382.3	17.8	1461	1.09	1.45	21.7	116.8	2891

varied in relation to the foodstuffs issued and does not contain a very high proportion of first-class protein. From the point of view of the present paper the important factor is that the staple article of food in the diet was maize meal, a food which also provides the largest proportion of the diets of these natives in their homes. In November 1944 it was found that the isolated position of the garrison and the fact that maize meal did not keep well

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that 0.4 per cent of the weight was made up of a contamination with the spores and sporangiophores of a variety of *mucor* (Plate 6, Fig 2). This is a surface contaminant of the rice which can be removed by washing. There were present also a trace of mouse faeces and webbed chrysalises of moth. Issues of this rice were made weekly to all units from a central store, and were accompanied by issues of ghee substitute which were obtained in bulk from a pool supply which at the same time was being issued to African

TABLE VIII

*Case Incidence in Relation to Care and Preparation of Rice in Units*

Unit	Number of men examined	Number of cases found	Doubtful cases present	Incidence per 1,000	Attention paid to rice
Group A					
1	400	4	+	11	{ Fair
	39	1	+		„
2	163	0	++	0	Good
3	130*	0	0	0	Excellent
4	54	6	+	111	Very poor
5	24	0	0	0	Fair to good
6	38	0	0	0	„ „
Group B					
7	314	37	++	85	Poor
Group C					
8 (a)	124	3	+	24	Fair
(b)	144	6	++	41	„
(c)	83	0	0	0	„
(d)	33	2	0	60	„

\* Mauritian troops only

troops elsewhere, among whom no cases of the disease had been reported. It is to be noted that this is in contradistinction to the rice supply which was confined to the troops of the affected garrison. It was found, however, that there was considerable difference in the amount of attention paid to the cleaning and care of the rice in individual units after its arrival from the central store. Storemen, quartermasters, and cooks were questioned and an attempt made to differentiate between those units which took little or no care and those which took particular care. The observations were then correlated with the incidence of cases in the units (Table VIII). It can be seen that an impression is conveyed that the units paying attention to the rice had a lower incidence than those which did not.

*Discussion*

Recent literature concerning the aetiology of the clinical syndrome which we describe favours two explanations for the condition, lack of thiamin or a toxin in the rice or in the oil used in its preparation. Clinical distinction between outbreaks caused by one or the other is almost impossible. Attempts have been made to differentiate between them by means of the blood sedimentation rate (Pasricha, Malik, and Lal, 1941) and the leucocyte count



TABLE VII  
*Daily Ration Scale, Mauritians*

Quantity issued (oz approximate)	Protein (gm)	Fat (gm)	Carbo-hydrate (gm)	Calcium (mg)	Iron (mg)	Vita-min A (i u)	Vita-min B1 (mg)	Ribo-flavin (mg)	Nicotinic acid (mg)	Vita-min C (mg)	Calories
Bread, white, 70% extraction	5	12	1	78	20	10	—	0.05	1.0	—	365
Rice, milled, raw	3	5	1	67	3	0.3	—	0.06	0.9	—	297
Fresh meat, low-grade	6	20	27	—	18	6.6	84	0.42	7.8	—	360
Milk, condensed, evaporated, unsweetened	10	3	4	5	110	0.2	144	0.16	0.2	—	64
Potatoes	1	1	—	5	2	0.2	—	0.03	0.3	2	21
Butter	2	—	47	—	8	—	2280	—	—	—	422
Fresh fruit	1	—	—	3	15	—	23	—	—	16	13
Fresh vegetables	2	—	—	—	24	0.2	60	0.02	—	22	4
Sugar	5	—	—	135	—	—	—	—	—	—	540
Totals	—	50	80	293	200	8.5	2591	0.49	10.2	40	2080

\* Direct estimation

(Annual Medical Reports, 1938, 1939) The medical authorities added considerably to the thiamin intake of this garrison as a preventive measure, but in spite of this precaution outbreaks occurred. Furthermore, the medical authorities were confident that treatment of these cases with thiamin also produced a beneficial result. In view of the evidence, therefore, we considered that the fact that the results of thiamin therapy were good was not sufficient

TABLE X

*Effects of Feeding Pigeons on Different Types of Rice*  
(Position at the end of 70 days)

	Initial number	Number died or sick, other causes	Number developed definite head retraction	Number ataxic, but no definite head retraction	Number in good condition
Group 1 (Highly polished rice)	4	2	2	0	0
Group 2 (Medium polished rice)	6	1	4	1	0
Group 3 (Rice alleged to have produced dropsy)	4	0	0	0	4

Note —All the birds which developed head retraction or ataxia were cured within four hours by the administration of thiamin

to warrant the assumption that lack of thiamin alone was the aetiological factor

If lack of thiamin was not the cause of the outbreak the alternative theory of a toxin must be examined. Such a toxin may be air-borne, water-borne, or food-borne. The distribution of cases within barrack rooms and within units was examined and there appeared to be no evidence that an air-borne toxin was likely to be the cause. Furthermore the peace-time medical authorities who had experienced similar outbreaks also considered that epidemics were not confined to particular barrack rooms, nor spread from person to person. In addition the epidemics always had a higher incidence among the troops located on the coastal strip where no communications exist between town and town unless they pass through central points where the disease was rare. It was possible that the toxin was water-borne, so the water-supply of the different parts of the garrison was examined. Units in Groups B and C (Table VIII) drew their water from independent wells having no connexion with one another. Units in Group A drew their water from the main town supply which was independent of the wells at B and C. The cases were distributed over all three areas. It therefore seemed to us impossible to incriminate water-supply. The toxin might have been food-borne, and this theory conforms with the ideas of most previous observers. The food of the garrison has already been described. If any food is to be incriminated then it should be rice, the main item in the African diet. This

(Dutt, 1925), both of which are alleged to be raised where a toxin has caused the condition and normal where lack of thiamin has been responsible. It can be seen from Table I and from the account of the syndrome that neither these findings nor any others clearly indicated the aetiological factors responsible for the epidemic. It was decided in the first instance to determine whether lack of thiamin was the cause of the outbreak. It can be seen

TABLE IX  
*Accepted Daily Minimum Levels of Thiamin Intake  
Comparison with Present Outbreak*

Authors	Mg thiamin per 1,000 calories	Total thiamin intake (mg)
Jansen and van Veen (1935)	—	0.303 to 0.6
Williams and Mason (1941)	0.5	—
Stiebeling and Phipard (1939)	0.303	0.91
League of Nations Committee on Nutrition (1939)	0.303	0.91
Bacharach and Drummond (1940)	—	1.06
Moran and Booth (1940)	0.75	—
Harris and Leong (1936)	—	0.6 to 0.91
Stepp, Kuhnau, and Schroeder (1937)	—	0.25 to 0.75
Baker and Wright (1936)	0.51	0.91
Present outbreak		
Europeans	0.377	1.093
Mauritians	0.25	0.49
Africans	0.320	0.926

(Table IX) that the total theoretical thiamin intake of the three races differed little, if anything the thiamin intake of the Africans was higher than that of the Mauritians, yet it has been noted that the outbreak was confined to African troops. The total thiamin intake of all three races would be considered adequate by most observers. The intake of thiamin in relation to the total calorie value of the diet is also recorded in Table IX. In all three instances the thiamin intake per 1,000 calories was of an order which has been thought by some to be sufficiently low to cause beriberi. Again no racial distinction can be drawn. It was next considered that a possible explanation might lie in the fact that the thiamin was in some way inactive. In order to test this hypothesis a number of pigeons was divided into three groups, the first fed upon highly polished rice only, the second upon milled rice whose thiamin content was 0.02 mg per oz, and the third solely upon the rice from the main stocks of the affected garrison. Table X shows the position at the end of 70 days. The only conclusion which can be drawn from this experiment is that the thiamin was active and adequate in relation to pigeons. It seemed to us improbable in view of the lack of other evidence to suppose that it was inactive in relation to man. The only evidence in favour of lack of thiamin appeared to be the results of the clinical trial recorded. In peace time, however, the area holds a garrison of native troops which are of different stock from those concerned in the present outbreak. Amongst these, explosive outbreaks of a similar clinical syndrome are common

taminated rice is much greater than in fresh rice cooked in the same way, for the same time, in the same pans. Secondly, the amount of heat acting on the rice, represented as the amount of rice cooked, appears to increase the amount of destruction. Confirmation of this was obtained by estimating samples taken from the top and bottom of the pan, the destruction was 58 per cent at the top and 86 per cent at the bottom. Thirdly, the time

TABLE XII

*Effect of Feeding Pigeons on Contaminated Rice Cooked*

	Initial number	Number died or sick, other causes	Number developed definite head reaction	Number ataxic, but no definite head retraction	Number in good condition
Group 1					
Rice alleged to have produced dropsy (uncooked) (See Table X)	4	0	0	0	4
Group 2					
Rice alleged to have produced dropsy (cooked)	4	0	3	1	0

Note —All the birds which developed head retraction or ataxia were cured within four hours by the administration of thiamin

for which the rice is cooked affects the amount of destruction. The average time for which the rice was cooked for the affected troops was 17 minutes. It is realized that these results are not statistically significant, but we nevertheless consider that they are suggestive. Fourthly, washing of the rice before cooking makes no difference to the thiamin destruction. Mention has been made (Table VIII) of the fact that units paying attention to the care of their rice had a lower incidence of the disease than those which did not. This included the washing of rice. Platt (1939) stated that, where rice is washed, the thiamin content is diminished and that outbreaks of beriberi are sometimes confined to communities which wash their rice clean. Our impression in this outbreak was to the contrary. There was, however, a great deal more than mere washing implied in the words 'care of rice'.

In order to confirm our theory that cooking had destroyed the thiamin, four pigeons which had previously been fed on 0.8 oz. of uncooked rice per diem, were fed on the same dry weight of the same rice cooked. The results are shown in Table XII. Not only did these pigeons develop signs of thiamin deficiency, but did so more rapidly than those on the polished rice (Table X). The pigeons on the polished rice developed the disease on the 29th, 30th, and 31st days, while on the cooked rice they developed the disease on the 18th, 20th, 22nd, and 25th days.

It is our opinion that while the thiamin content of the rice appeared to be adequate to prevent beriberi, some other substance had developed in the rice which, during the process of cooking, destroyed the thiamin so that the cooked grain was capable of producing beriberi. Thiamin chloride is

also conforms with accepted ideas in similar outbreaks. The peace-time medical authorities reached the conclusion in 1939 that the abolition of rice in the diet seemed to be the only method of preventing such epidemics (Annual Medical Report, 1939). There is nothing inconsistent on epidemiological grounds with the theory that a toxin which was present in the rice acted upon the subjects. Such a hypothesis fits all the known facts and

TABLE XI

*Deterioration of Thiamin Content of Rice after Cooking*

Sample				Amount of rice cooked (gm)	Time of cooking (min)	Percentage loss of thiamin
Fresh rice				150	20	30
" "				50	20	31
Contaminated rice				150	20	60
" "				150	20	58
" "				100	20	66
" "				100	20	60
" "				50	20	76
" "				50	20	88
" "				50	15	53.5
Contaminated rice washed before cooking				50	20	76
" " " "				50	15	63
" " " "				50	15	52
" " " "				50	20	63
" " " "				50	15	52
Contaminated rice washed only				50	0	13.5
" " " "				50	0	18.2

*Mean losses (contaminated rice cooked)*

After 20 minutes cooking = 67.5%.

" 15 " " = 55.0%.

*Mean loss (total) = 64%*

After 20 minutes cooking 150 gm = 59%.

" " " 100 " = 63%.

" " " 50 " = 75.7%.

Note —Standard method of cooking and same pans used throughout  
Contaminated rice as supplied to affected troops

would label the outbreak as one of epidemic dropsy. Students of similar previously described outbreaks have reached the same conclusion as a result of epidemiological studies only. Experimental evidence that such a toxin exists is, however, scanty, and evidence that it acts directly upon man, as far as we know, almost non-existent (Lal, Das Gupta, Mukherj, and Adak, 1941). It appeared to us, however, that the evidence in this, as in similar outbreaks, was negative and hence unsatisfactory. The same epidemiological evidence would fit an alternative theory that the toxin acted upon the thiamin rather than upon the subject. In order to examine this hypothesis samples of the contaminated rice were cooked and their thiamin content re-estimated. The results are recorded in Table XI. It will be seen from a study of the Table that firstly, the destruction of thiamin in the con-

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known to be destroyed by alkaline solutions and becomes increasingly unstable at pH more alkaline than 6.0. The pH of the water in which our experiments were undertaken ranged from 6.2 to 6.4. The changes in pH of the water before and after the rice was cooked were negligible. Such a pH should not give a high rate of thiamin destruction. More important than this in our opinion is the fact that the destruction of thiamin in fresh rice when cooked in the same water was very much lower than that in the contaminated rice, and if the pH of the water accounted for the destruction this should not be so. The importance of our observations is that outbreaks of epidemic dropsy should, in our opinion, be regarded as beriberi until it can be shown that the thiamin is not destroyed in the process of cooking. It is of little value to estimate the thiamin content of uncooked rice and to calculate from it the supposed thiamin intake of the subjects. It is possible indeed that only one aetiological factor exists to account for both these diseases, namely thiamin lack, although many more observations will have to be made before such a hypothesis can be established. We have attempted during this discussion to follow our own trends of thought during the investigation. At first it seemed as though there was a typical outbreak of beriberi, although its explosive character suggested that it might be epidemic dropsy. Later as the thiamin content of foods was estimated and as epidemiological facts came to light, it seemed as though it was an epidemic of dropsy. Later still we considered that, although according to accepted standards the outbreak was consistent with one of epidemic dropsy, the toxin had not operated directly upon the subjects but rather upon the thiamin.

### *Summary*

1 An outbreak of a syndrome clinically indistinguishable either from beriberi or epidemic dropsy is described amongst troops in an isolated garrison. Three races were represented, European, Mauritian, and African. The outbreak was confined to African troops.

2 The diets of all three races are described.

3 Investigations were carried out to elucidate the aetiological factors responsible.

4 Epidemiologically the outbreak was indistinguishable from the accepted descriptions of epidemic dropsy usually attributed to the presence of a toxin in the food.

5 Evidence is produced that in this epidemic the thiamin was destroyed during cooking of the old contaminated rice.

6 It is considered possible that epidemic dropsy and beriberi are the same disease, and probable that some outbreaks, similar to the one described, are caused by destruction of thiamin in cooking the food, rather than by its absence.

We would like to express our thanks to Brigadier R. Cormack, Deputy Director of Medical Services, East Africa Command, and to the Garrison

Commander, Colonel W R Wilson, to Lt-Colonel R W Chapman, R A M C, and Captain Hailwood, Hygiene Officer, for the kind way in which they offered us facilities, to Major H J Heathcote, R.A M C, for assistance with the pigeon experiments, and finally to Mrs E D F Davis for work on the tables and manuscript

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FIG 1 Illustrating pitting oedema of the legs

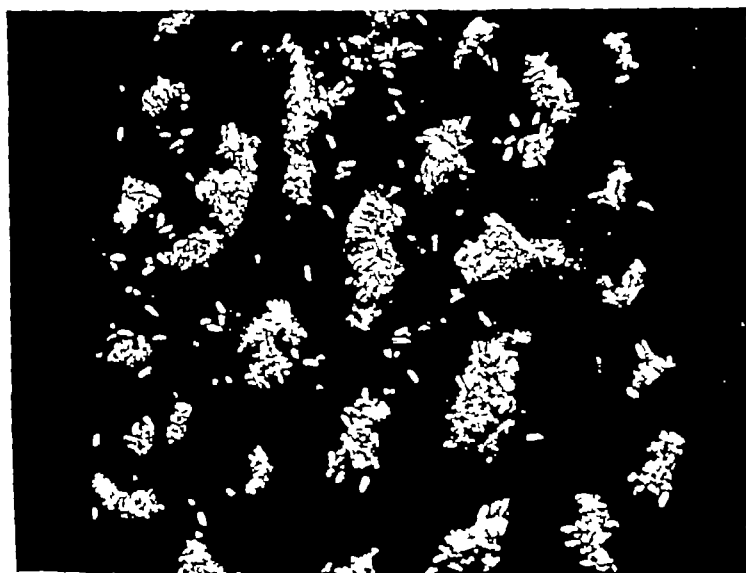


FIG 2 Illustrating the clumping of rice grains with  
contaminating *Mucor*



# THE HEART IN ANAEMIA<sup>1</sup>

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With Plates 7 to 9

## *Introduction*

ABNORMAL signs in the cardiovascular system, together with symptoms which might arise from it, have for many years been recognized in anaemia. In the early part of the nineteenth century Laennec (1846) and Hope (1839) both observed cardiac murmurs of inconstant character in chlorosis, and later, Bamberger (1857) and Friedreich (1861) commented on the pathological findings of fatty infiltration and degeneration, together with dilatation and increased weight of the heart. More comprehensive studies of haemic murmurs were made by Irvine (1877) and Barrs (1891), both of whom found them to be systolic in time, usually situated at the base of the heart, and only to be distinguished from the murmurs of valvular disease by their disappearance after treatment of the anaemia. Presystolic and diastolic murmurs in severe anaemia without pathological evidence of valvular disease were found by Friedreich (1861), von Noorden (1891), Sahli (1895), and Cabot and Locke (1903). Subsequent authors (Goodhart, 1880, Kraus, 1905, Oertner, 1923, Gunewardene, 1933) have confirmed these findings, and anaemia is now established as a cause of cardiac murmurs which normally disappear when the blood is restored by treatment (White, 1937). It has been generally believed that the murmurs of anaemia are caused by associated cardiac enlargement, but some writers, notably Sahli (1895) and Gard (1944), have believed that a decreased viscosity of the blood was an important factor. Abnormalities of the heart sounds have attracted little notice, although Grunberg (1930) noticed accentuation of the apical first sound, and Klinefelter (1942) later recorded a presystolic element in this sound by stetho-cardiogram in sickle cell anaemia, but reports of additional heart sounds, giving a triple cardiac rhythm usually described as 'gallop' in type, have been made by Gunewardene (1933) and others (Bouchut and Froment, 1934, Marchal, Soulié, and Roy, 1935, Sharer and Pietrafesa, 1940) in severe anaemia, usually with heart failure.

Enlargement of the heart appears to have been first noticed in pathological studies. Later authors, notably Cabot and Richardson (1919), Bouchut and Froment (1934), Bouchut, Froment, and Bonnet (1934), Grunberg (1930), and Reid (1923), have stressed the increased weight of the heart in various

<sup>1</sup> Received October 16, 1945

types of anaemia and have described hypertrophy and dilatation, in addition to the fatty changes Cabot and Richardson were careful to exclude evidence of hypertension or arteriosclerosis, but did not always state detailed criteria of hypertrophy, so that the possibility that fatty changes by themselves caused an increase in the weight of the heart and the thickness of the muscle should be remembered. Microscopic studies which support the finding of true hypertrophy have been made (Fahr and Ronzone, 1922, Nemet and Gross, 1936), although some of these have been in sickle cell anaemia, in which thromboses in the pulmonary circulation are likely to have been important (Diggs and Ching, 1934, Hein, McCalla, and Thorne, 1927, Steinberg, 1930, Yater and Hansmann, 1936). The first clinical studies of enlargement in anaemia were those of Starke (1863) and Gautier (1899) who reported enlargement, determined by an increased cardiac dullness on percussion, in chlorosis, and claimed that it sometimes regressed after treatment of the anaemia. Radiological evidence of enlargement was first found by the early workers in this field in Germany and Vienna, for Moritz (1913) demonstrated it by orthodiagrams in severe secondary anaemia, and showed that the heart became smaller after treatment. Shortly afterwards Zondek (1919) and Assmann in 1922 (Assmann, 1934) published similar findings in chlorosis and in anaemia from *Bothriocephalus latus* infestation, and Dietlen (1923) in a case of pernicious anaemia showing enlargement of the heart in a teloradiogram. Later Goldstein and Boas (1927) published teloradiograms showing enlargement in anaemia, and distinguished a left sided type mainly involving the left ventricle, and a mitral type with a straight left border which they ascribed to a left auricular salient. Although Ball (1931) used successive teloradiograms to demonstrate in a woman, anaemic from uterine haemorrhage, an enlargement which became smaller with improvement in the blood picture, no considerable study was made by this method until Porter (1937) published his findings in 18 cases of chronic hookworm anaemia. He found enlargement in all his cases, as judged by the cardiothoracic ratio and the prediction formula of Hodges and Eyster, and showed that this diminished in the majority, although still persisting in some, when the anaemia had been treated. It was believed that these findings indicated a primary cardiac dilatation which could be lessened by treatment of the anaemia, but might otherwise lead to an irreversible hypertrophy. Shortly after this, Tung, Bien, Ch'u, and Wang (1937) made similar studies in 10 cases of very severe and long standing anaemia, mostly hypochromic, and found enlargement in nine. In eight the heart became normal in size after treatment. There have been other observations of cardiac size in hookworm anaemia (Gupta, 1942, Heilig, 1942), sickle cell anaemia (Diggs and Ching, 1934, Klinefelter, 1942, Yater and Hansmann, 1936), and Cooley's anaemia (Nemet and Gross, 1936), together with case reports in various types of anaemia (Dassen and Parodi, 1936, Fahr and Ronzone, 1922, Sharer and Pietrafesa, 1940), and in spite of criticism (Parsons and Wright, 1939) of the radiological technique in some of these it can now be recognized that cardiac

enlargement which may regress after treatment can occur in anaemia (Zdansky, 1939, Roesler, 1943) It has been suggested that myocardial anoxaemia is the cause of the cardiac enlargement in anaemia (Lewis and Drury, 1923) and both the enlargement found in man after residence at high altitudes, and the clinical and pathological changes found in animals under conditions of low oxygen tension (Campbell, 1927, Forman and Daniels, 1930, Van Liere, 1927, Ludke and Schuller, 1910) support this view Recent work, however, has shown that there are gross disturbances of the circulation in anaemia and these may be even more important in producing cardiac enlargement Outstanding among them is a raised cardiac output which has been repeatedly demonstrated by the older respiratory methods (Dautrebande, 1925, Grollman, 1932, Nielsen, 1934, Richards and Strauss, 1928, Stewart, Crane, and Deitrick, 1937), and more recently by Sharpey-Schafer (1944) using intracardiac catheterization for the determination of the oxygen content of the venous blood Sharpey-Schafer has also found a raised venous pressure by this method and claims that it is an important factor in raising cardiac output It has been shown (Eyster and Middleton, 1924, Sharpey-Schafer and Wallace, 1942) that cardiac enlargement can be produced by overloading of the circulation, and that conversely a decrease in cardiac size can follow massive haemorrhage (Dietlen, 1923, Meek and Eyster, 1921) so that there are grounds for believing that changes in venous pressure may exert an appreciable influence on the heart in anaemia

Cardiac pain like that of angina pectoris was first recognized in anaemia by Herrick and Nuzum (1918), and later by Coombs (1926) Since then it has been fairly frequently reported in the literature (Bernstein and Ginzburg, 1942, Bloch, 1937, Elliot, 1934, de Matteis, 1936, Pickering and Wayne, 1933, Stalker, 1937, Vatcher, 1939, Zimmerman and Barnett, 1944), Willus and Giffin (1927) in particular finding evidence of it in the records of 43 out of 1,560 cases of pernicious anaemia, where it was closely associated with other cardiac signs, tachycardia, murmurs, and enlargement The descriptions have shown the pain to be like that of angina pectoris, except that it does not often radiate to distant areas, and that it is seldom the presenting symptom, being often overshadowed by dyspnoea, palpitation, and lassitude (Froment and Guiran, 1939) In many of the reported cases appropriate treatment of the anaemia has abolished the pain Sometimes evidence of coronary artery disease has been found *post mortem*, but not always, for Cabot (1926) and Elliot (1934) have both reported cases where the coronary arteries have been healthy In spite of this, many writers have denied that anaemia alone can cause cardiac pain

~ Electrocardiographic abnormalities in anaemia seem to have been first reported by Ussoff (1911), and latterly by Coombs (1926) and Serf (1929), each of whom described lowered T waves Turner (1932) found low-voltage curves in severe anaemia, and Elliot (1934) S-T segment depression in a single fatal case where the coronary arteries were normal *post mortem*

Transitory prolongation of the P-R interval in anaemia was described by Pickering and Wayne (1933). Later authors (Dassen and Parodi, 1936, Ellis and Faulkner, 1939, de Matteis, 1936, Porter, 1937) have studied the electrocardiogram, and Bloch (1938) found abnormalities in 47 out of 83 patients, namely low-voltage curves, R-T segment depression, and flattening or inversion of the T waves in one or more leads. A return to normal of the electrocardiogram was sometimes observed after treatment, although this did not always occur even where there was no reason to suspect other forms of heart disease. Szekely (1940) also studied a considerable series of cases and his findings agreed substantially with those of Bloch. Neither of these authors was able to correlate closely the incidence of electrocardiographic abnormalities with the severity of the anaemia, and both believed that the youth of some of their patients excluded coincident coronary artery disease. Other observers have reported negative electrocardiographic findings in studies of anaemia patients numbering from 12 to 113 (Hochrein and Matthes, 1935, Reid, 1923, Smith, 1933). It has been generally agreed that myocardial anoxaemia would account for these changes, specially since they have been reproduced, often accompanied by cardiac pain (Levy, Barach, and Bruenn, 1938), in man by exposure to low atmospheric oxygen tension (Greene and Gilbert, 1921, Lewis and Mathison, 1910, Mathison, 1910, Rothschild and Kissin, 1932), but this explanation cannot hold good for other changes such as S-T deviation and T wave inversion which have been found after massive haemorrhage (Aschenbrenner, 1935, Bloch, 1937, Marchal, Soulié, and Roy, 1935, Master, 1942, Scherf and Klotz, 1944, Scherf, Reinstein, and Klotz, 1941). In these cases recovery, either spontaneously, or after infusion of saline or blood, has suggested that they were caused by disturbances of the blood-volume and the general circulation (Marchal, Soulié, and Roy, 1935), a view in agreement with the findings in experimental bleeding of animals (Marchal, Soulié, and Baugé, 1938, Radnai, 1935). Although the symptoms and signs of anaemia have often simulated those of other kinds of heart disease with failure (Coombs, 1926, Gunewardene, 1933), congestive failure seems to be uncommon. Cabot (1926) found it *post mortem* in 12 out of 23 fatal cases of pernicious anaemia with large hearts, and it was also present in six of Tung, Bien, Ch'u, and Wang's (1937) nine patients. It was observed by Bouchut, Froment, and Bonnet (1934) and Bouchut and Froment (1934) in association with gallop rhythm, and successfully treated with digitalis, an experience not shared by others.

In spite of the literature reviewed above, comprehensive clinical studies of the heart in anaemia are not numerous and have mostly dealt with selected types of anaemia, or cases of great severity (Grunberg, 1930, Strieck, 1924, Zuckerstein and Pozniak, 1935). It seemed desirable, therefore, to undertake an investigation into the common anaemias of moderate severity, the more so as no such work had been found in the literature of this country, although a similar study by Ellis and Faulkner (1939) has been made in the United States of America.

*Personal Observations*

*Material* All cases observed were seen at the London Hospital during the last two years, and were chosen because their presenting symptoms and signs led to a general diagnosis of anaemia, only those being excluded where the anaemia was caused by some mortal illness such as carcinoma or leukaemia. Care was also taken to reject those with coincident nutritional or endocrine disorders, such as myxoedema, or with a raised diaphragm from any cause, since these factors are known to interfere with the estimation of the size of the heart. The liability of anaemia to simulate other types of heart disease makes it difficult to exclude organic cardiac lesions with certainty, but all patients with known or reputed valvular disease, or hypertension, were rejected. In all, 34 patients were included, 26 female and 8 male, their ages varying from 30 to 71 years with an average of 40 years. In 27 the anaemia was hypochromic with or without chronic bleeding, usually from the gastro-intestinal tract, in five it was Addisonian, and in two refractory. The severity of the anaemia, though never extreme, varied from moderate to considerable, with initial haemoglobin values of from 22 per cent to 55 per cent. Two cases seemed to fall outside these limits, but one with a haemoglobin of 16 per cent was seen after an acute exacerbation of a chronic anaemia, and the other with a haemoglobin of 62 per cent had previously shown a much lower figure. Apart from an occasional leucopenia there were no other significant changes in the blood count. Haemoglobin was estimated by the Sahli method. The duration of the anaemia was hard to estimate because of the insidious character of the symptoms, but in the majority it was measured in months, although in three it was of a shorter duration with a minimum of one week, and in six it had lasted for years, with a maximum of 20 years. The main features of the cases are summarized in Table I.

All the patients were treated in bed, except five who were ambulant. Observations on the pulse rate, blood-pressure, and heart were made at the beginning of treatment, at an intermediate stage, and at the end, the exact time depending on clinical progress and the blood count. The size of the heart was determined by teloradiograms, and electrocardiograms were taken initially in most cases and repeated later in some. The findings so obtained were correlated with a blood count made on the same day. The only treatment given was that appropriate to the anaemia, almost invariably the exhibition of iron or liver, which were given in dosage sufficient to bring about an improvement, or to justify their withdrawal as ineffective. The observations were continued until a haemoglobin level of 90 to 100 per cent was reached, except when the cardiac findings were negative, when they were not always prolonged beyond 80 per cent. The time taken was generally several months, but sometimes extended over a year or more.

*Symptoms* The general symptoms of anaemia, such as lassitude, pallor, and anorexia, were almost always present, but only those suggestive of



cardiac disease, dyspnoea, palpitation, and cardiac pain, will be discussed. Dyspnoea was the most common symptom, occurring in all but two patients, it was severe in three and slight in five, and was never present at rest. There was never orthopnoea or paroxysmal dyspnoea, indeed the most breathless patient could lie flat in bed with only a single pillow, in contrast

TABLE I  
*Main Features*

No	Age	Sex	Diagnosis	Duration	Initial haemo-globin %	Final haemo-globin %	Period of observation
1	60	M	Addisonian anaemia	3 years	30	103	1 year
2	33	M	Hypochromic "	1 week	47	97	6 weeks
3	54	M	Addisonian "	8 months	38	104	8 months
4	71	F	Hypochromic "	1 year	33	86	4 "
5	14	F	" "	18 months	40	95	4 "
6	34	F	" "	7 years	40	92	2 "
7	10	F	" "	4 months	48	93	6 "
8	15	M	Refractory "	10 "	30	80	5 "
9	42	F	Hypochromic "	4 "	50	97	10 "
10	32	F	Refractory "	5 years	45	30	2 "
11	50	F	Hypochromic "	1 year	53	97	4 "
12	30	F	" "	1 month	40	80	1 month
13	37	F	" "	2 months	37	100	15 months
14	32	F	" "	6 "	32	87	5 "
15	70	M	" "	5 weeks	53	72	5 weeks
16	53	F	" "	1 month	52	85	6 "
17	56	F	Addisonian "	?	62	92	2 months
18	31	F	Hypochromic "	3 months	48	103	11 "
19	40	F	" "	2 years	52	99	1 year
20	37	F	" "	3 months	22	92	9 months
21	40	M	" "	5 weeks	55	97	10 "
22	52	F	Addisonian "	3 years	35	100	18 "
23	42	F	Hypochromic "	4 months	27	101	3 "
24	34	F	" "	5 years	24	98	10 "
25	40	F	" "	1 month	44	93	21 "
26	38	F	" "	9 months	40	101	4 "
27	48	F	" "	6 "	27	103	3 "
28	53	F	" "	20 years	24	79	16 "
29	51	M	" "	3 months	30	80	2 "
30	40	F	" "	10 "	37	97	15 "
31	48	F	" "	18 "	32	95	8 "
32	51	M	Addisonian "	3 "	37	101	3 "
33	57	F	Hypochromic "	1 year	59	95	7 "
34	45	F	" "	18 months	33	112	11 "

with patients suffering from frank heart failure. There was no relation between the severity of the dyspnoea and the other cardiac signs. No abnormal physical signs were present in the lungs, and there was no definite radiological evidence of pulmonary congestion. Treatment of the anaemia always relieved the symptoms. Palpitation was the symptom next in frequency, being found in 18 patients and only on exertion. It usually implied an increase in the rate as well as the force of the cardiac impulse. Cardiac pain similar to that of angina pectoris was present in eight out of 34 cases, that is in almost a quarter of the series. In three it was the presenting symptom, but in the others it was overshadowed by lassitude and dyspnoea. The character of the pain differed in no way from that of angina pectoris,

for it was substernal, tight, and constricting, although radiation to the left arm and back was noted only twice, it was present only on exertion, and often interfered with the patient's daily life. Four other patients complained of tightness in the chest, without pain, but brought on by exercise and quickly relieved by rest, so that it seemed to differ only in severity from the more typical anginal pain. Complete and early abolition of the pain followed treatment of the anaemia in every case except one, where it persisted for some three months after the blood had become normal, and then ceased.

Ten of these patients were women and two men, three were 50 years or over, but five were 40 or less, and the youngest was 31. Hypertension was never present at the first examination, but in two of the older patients, a man and a woman, it was manifest when the anaemia had been treated. Associated cardiac enlargement was present in seven cases. Electrocardiographic changes, which will be discussed later, were found in three patients and were absent in six. Since so many workers have believed that anaemia alone cannot cause cardiac pain, these findings are significant. In the three older patients, though pain was abolished by treatment, one could not exclude underlying coronary artery disease (angina pectoris), specially since hypertension was present in two and peripheral arteriosclerosis in one. In the five younger patients who had no hypertension, and were of an age when angina pectoris in women is admittedly uncommon, there was good reason for believing that the pain was due to the anaemia alone. The similar experience of Bloch (1938) and the negative necropsy reports are so definite that it is difficult to understand on what grounds they can be doubted, indeed the findings are striking enough to suggest that in any woman under 40 without hypertension, and complaining of cardiac pain, the cause may be an unrecognized anaemia. Intermittent claudication was present in two patients, both men over the age of 50 years. Although the presence of hypertension in one, and the absence of dorsalis pedis pulsation in the other, suggested arteriosclerosis as the cause, the improvement after treatment of the anaemia was considerable.

*Physical signs* The usual signs of anaemia with pallor of skin and mucous membranes were found. Changes in the tongue and finger-nails were also frequently present, and slight degrees of oedema in the sacral area and the lower limbs were seen occasionally, but there was never gross anasarca, ascites, or pleural effusion. The cardiovascular signs will be specially discussed and are summarized in Table II. In the initial stages the pulse-rate was variable and easily influenced by exertion, and there was usually a moderate tachycardia (below 120), even at rest. In two patients the pulse was collapsing in character despite the absence of aortic incompetence, otherwise no abnormal features were observed. The resting blood-pressure in all patients was initially within normal limits, with an average of 135 mm of mercury systolic, and 70 diastolic, while after treatment there was an average of 140 systolic and 80 diastolic. The chief alteration was a rise in

TABLE II  
Cardiac Signs

Case No	Before treatment					After treatment				
	Pulse	Blood-pressure	Murmurs		Enlarge-ment	Pulse	Blood-pressure	Murmurs		Enlarge-ment
			Mitral	Pulmonary Aortic				Mitral	Pulmonary Aortic	
1	92	110/70	+	—	—	70	110/10	—	—	—
2	80	110/70	+	—	—	64	115/70	—	—	—
3	110	120/65	+	—	—	70	140/85	—	—	—
4	84	90/60	+	—	—	80	120/65	+	—	—
5	96	160/80	+	+	—	70	125/90	+	+	—
6	84	120/80	+	—	—	70	130/70	+	—	—
7	92	150/80	+	+	—	70	120/70	+	—	—
8	100	120/80	—	—	—	—	—	—	Died	—
9	76	130/80	+	—	—	64	110/80	—	—	—
10	68	110/70	+	—	—	68	110/70	+	—	—
11	84	160/80	—	—	—	70	125/90	—	—	—
12	78	120/70	—	—	—	80	120/70	—	—	—
13	80	115/70	+	*	—	68	125/80	—	—	—
14	112	120/70	—	—	—	70	125/90	—	—	—
15	80	150/85	+	—	—	70	140/70	—	—	—
16	84	135/85	—	—	—	74	135/80	—	—	—
17	—	—	+	+	—	—	—	—	?	—
18	80-90	150/70	+	—	+	74	130/80	+	—	—
19	92	135/70	+	—	—	60	110/70	—	—	—
20	104	150/80-0	+	—	Doubtful	70	130/80	+	—	—
21	80	120/70	+	—	Doubtful	70	140/80	+	—	—
22	90	140/55	+	—	—	78	180/100	+	+	—
23	100	120/65	+	+	—	76	140/90	+	+	—
24	76	160/70	+	+	—	80	145/80	+	—	—
25	80	160/90	+	—	—	70	160/90	+	—	—
26	80	150/55	+	—	—	80	160/80	—	—	—
27	80	135/75	+	+	—	80	150/95	+	—	—
28	—	—	+	+	—	—	—	+	+	—
29	80	120/60	+	—	—	80	140/80	+	—	—
30	80	120/80	+	—	—	80	150/60	+	+	—
31	84	120/70	+	—	—	80	160/90	+	—	—
32	96	130/80-50	+	+	Doubtful	64	130/70	+	—	—
33	70	160/90	+	+	—	64	210/90	+	—	—
34	80	160/80	+	+	—	80	170/95	—	—	—
							160/80	—	—	—

+ Presystolic murmur in addition

\* Early diastolic murmur in addition

\* Early diastolic murmur in addition

† Prosystolic murmur in addition

Doubtful  
" "  
" "

both diastolic and systolic pressure. The former was the more notable, as a difference of more than 10 mm. was seen in 15 patients and a rise of 5 mm. in four. Three showed considerable changes, in one the initial blood-pressure rose from 140/55 to 180/100, in another from 130/55 to 200/100, and in a third from 130/60-0 to 130/90. In this last patient, in whom there was also cardiac enlargement and a third heart sound at the apex, the pulse was collapsing, and the diastolic end-point was difficult to estimate, as although there was a decrease in their intensity at 60 mm. the sounds were heard loud and clear down to the zero level, as in severe degrees of aortic incompetence. On clinical grounds the finding of latent hypertension, becoming apparent in two patients after treatment, is important, as it might cause confusion in diagnosis, specially if cardiac enlargement which might otherwise be attributed to the anaemia were present.

Alterations in the character of the heart sounds were noticed in about half of the cases. The mitral first sound was frequently prolonged and accentuated, sometimes resembling that found in mitral stenosis, but more striking was the presence in eight patients of an additional third heart sound at the apex. This latter finding, which was sometimes recorded by the phonocardiograph (Plate 7, Fig 2), must be considered abnormal since all the patients were over 30 years of age (Evans, 1942). Both of these signs were associated with a moderate tachycardia, and disappeared when the pulse-rate slowed. Cardiac enlargement was found in all but two of those with third heart sounds, and sometimes in addition there were signs of right heart failure, venous distension, hepatic engorgement, and electrocardiographic abnormalities. Cardiac murmurs were heard in 30 of the cases, and none in four. They were always systolic in time, except in one case which showed an early diastolic murmur, and another a presystolic murmur. An attempt has been made to classify the murmurs according to their intensity, the term faint indicating a murmur which would not have excited comment in the routine examination of a healthy subject, moderate where further investigation would have been needed, and rough where there would have been a strong suspicion of organic valvular disease. Six murmurs were described as faint, 16 as moderate, and nine as rough. In 29 cases murmurs were heard at the apex, in 21 in the pulmonary area, and in six in the aortic area. Twenty had murmurs at more than one site, mitral and pulmonary in 14, mitral, pulmonary, and aortic in six. An apical murmur alone was present in nine cases and a pulmonary murmur in one. Aortic murmurs were always accompanied by both pulmonary and mitral murmurs. The louder murmurs were heard in two or often three areas, and the softer in single areas, generally the mitral. It was also usually found that where multiple murmurs were present they were loudest at the apex, then in the pulmonary area, and least loud in the aortic area. The murmurs were usually diminished in the erect position, specially when their intensity had lessened after treatment. In nine patients murmurs, though never accompanied by thrills, were loud enough to raise a suspicion of valvular disease, although their distribution

made such a diagnosis unlikely. Twice an apical murmur with an unusually loud first sound, and an additional third heart sound, strongly suggested mitral stenosis, and sometimes it was difficult to exclude aortic stenosis when the murmurs in the aortic area were particularly loud. The fainter murmurs presented less difficulty, although occasionally suggesting a slight mitral lesion. The two diastolic murmurs, one late or presystolic at the apex, and the other early in the fourth left interspace near the sternum, led to diagnoses of mitral stenosis and aortic incompetence respectively until their disappearance with treatment indicated their haemic origin. The incidence of murmurs was not directly related to the severity of the anaemia, for they were often conspicuous when it was slight and absent when it was considerable. The duration of the anaemia seemed more important.

The widespread belief that cardiac enlargement is the cause of haemic murmurs was not confirmed, since their association was inconstant, and noticeable murmurs might be heard where the heart was normal in size, and might be absent where there was enlargement. The effects of treatment were also different, for enlargement usually diminished rapidly while murmurs persisted longer. All murmurs were lessened in intensity by treatment, and the majority disappeared or became negligible when the blood was normal, a few, however, persisted for some months after this before finally disappearing. In short, murmurs might occur with any degree of anaemia, and might be difficult to distinguish from the signs of valvular disease, especially mitral and aortic disease, but the recognition of anaemia necessitated caution until the treatment was complete, when the diagnosis could be established with certainty. Phonocardiograms were made in a few cases. They showed murmurs later in systole than those of mitral disease.

*Electrocardiography* The standard limb leads were recorded in 25 patients on one or more occasions. Sometimes chest leads were used and have been designated according to the nomenclature recommended in 1938 by the Committees of the American Heart Association, and the Cardiac Society of Great Britain and Ireland.<sup>2</sup> In 18 cases the standard electrocardiogram was normal, and in seven re-examined after treatment there was no change. Minor changes, flattening of the T wave in one or more leads, were observed in five cases. Two of these returned to normal after treatment, but the others were unaltered. In two patients the electrocardiogram was grossly abnormal. In one of them, a woman of 42 years with hypochromic anaemia (haemoglobin 50 per cent) and a history of cardiac pain on exertion, the electrocardiogram (Plate 7, Fig 3*b*) showed a T wave low in lead I, and inverted in II and III. The T wave was also flat in the chest lead CR<sub>1</sub> and inverted in IVR. Haemic murmurs were present, but no enlargement, and the blood-pressure was normal. In spite of successful treatment of the anaemia with abolition of the pain, the electrocardiogram was unchanged.

<sup>2</sup> IVR indicates an exploring electrode at the apex paired with an indifferent one upon the right arm. CR<sub>1</sub> indicates an exploring electrode in the 4th right interspace near the sternum paired with one upon the right arm.

even on re-examination a year later. In the other, a woman of 40 years with hypochromic anaemia (haemoglobin 40 per cent) from chronic uterine haemorrhage, and mild cardiac pain, the electrocardiogram (Plate 7, Fig 3a) showed T low in lead I, flat in II, and inverted in III. In the chest lead IVR T was upright, but it was inverted in CR<sub>1</sub>. Generalized cardiac enlargement and haemic murmurs were present, and the blood-pressure was normal. The anaemia was successfully treated and the pain and murmurs disappeared, but the size of the heart and the electrocardiogram were unchanged when the patient was re-examined 15 months later. It is of course not possible to exclude additional coronary artery disease in these patients in spite of their sex and age, but neither the history nor the electrocardiographic patterns suggested cardiac infarction, and it seems more likely that anaemia alone was responsible for the abnormalities. In two other patients with anaemia and cardiac signs there was inversion of T in the chest lead CR<sub>1</sub>. This is abnormal and a finding seen in right heart failure. Further study with this lead might have been helpful.

*Cardiac enlargement* The size of the heart has been studied by means of successive teleradiograms taken, as indicated previously, at the beginning of treatment, and subsequently at intervals determined by the progress of the patient. The difficulties of comparing heart size by this method are not negligible since several variables must be controlled if results are to be valid. Alterations in the height of the diaphragm can affect the size of the heart shadow, which can also be distorted by variations in the centering of the tube upon the patient in films taken at different times. In strictly comparable films the patterns of the bony thorax and the diaphragm should exactly coincide (Roesler, 1943). This is not always easy to achieve, but by careful positioning in all planes of the patient upon a fixed stand, and by preliminary instruction in breathing, errors from these causes were reduced to a minimum. A relatively long exposure, at least 0.3 sec., helped to counteract the effects of different phases of the cardiac cycle. The presence or absence of enlargement has been assessed from a visual impression of the size of the heart in relation to the bony thorax, as seen in teleradiograms and on cardioscopy. Though making no claim to exactness this method is convenient and of sound practical value, while the various prediction formulae which have been calculated to allow for variations in height and body weight are open to criticism (Levy, Stroud, and White, 1943). Also it seemed that the best proof that a heart had once been enlarged because of anaemia would be the demonstration of a decrease in size when the condition of the blood had improved. Twelve of the 34 hearts studied by these methods showed enlargement, 16 were considered normal in size and shape, while in six enlargement was doubtful. Of the last group, two showed a decrease in size after treatment of the anaemia, thus proving that previously they had been enlarged. Nine of the cases with large hearts showed a reduction in cardiac size after treatment, one other showed an apparent decrease which could not be properly assessed because of variations in the height

of the diaphragm, two were unchanged. Enlargement was usually generalized and, although the left ventricle was often prominent, fullness in the conus region sometimes gave a straight left border to the heart, while it was not

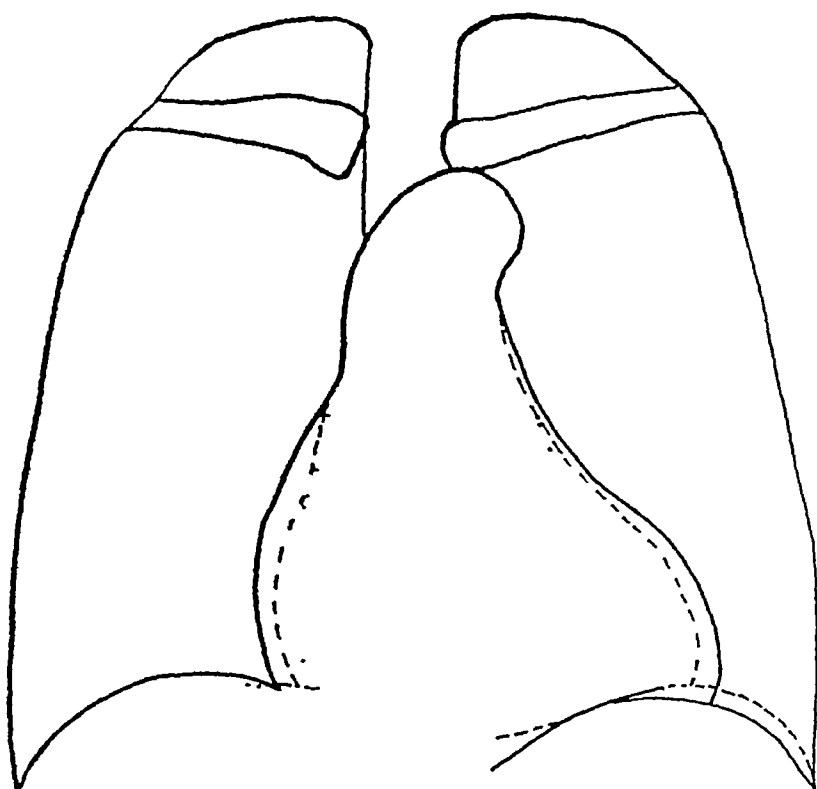


FIG 1 A woman, aged 34 years. Hypochromic anaemia. Tracings from superimposed teleroadiograms to show reduction in heart size on successive occasions.

Continuous line	13 12 43	Haemoglobin	24	per cent
Interrupted line	29 12 43	"	67	"
Dotted line	15 2 44	"	98	"

possible to distinguish clearly the left-sided and mitral types which have previously been described.

The reduction in cardiac size which was observed in 11 cases can be seen in juxtaposed teleroadiograms (Plate 8, Fig 4, and Plate 9, Fig 5), but diagrams traced from films taken on different occasions and superimposed upon each other (Fig 1) are more easily compared. The reduction in size was always generalized, but in addition any straightening of the left border which had been initially present was replaced by a normal concavity. Although exact measurements were not attempted, it may be said that decreases in transverse diameter varied in amount from 0.7 cm to 1.8 cm. Does the heart return completely to normal? With our present methods it

is hard to say, but it was believed to do so in eight of the 11 cases where it had become smaller. Three remained doubtful and have been described as full size, that is on the upper limits of normality. Definite enlargement persisted in three cases, there was no change in two, and a doubtful reduction in one. The explanation of this is not clear except that in one the patient

TABLE III

*Differences in the Haemoglobin Levels at which Enlargement  
Decreased and Murmurs Disappeared*

Case No	Haemoglobin percentage at which enlargement decreased	Haemoglobin percentage when murmurs disappeared
18	59	103
19	52	97
20	65	100 (still present)
21	85	101
22	67 and 98	98
23	84	93
24	87 and 101	101
25	68	68
31	85	85
32	64	101
33	95	95
34	99	99

refused further treatment while still anaemic, and in another there was a rheumatic history. In the third the only obvious reason was a prolonged anaemia of 20 years' duration, a conclusion subsequently confirmed *post mortem*. There was no direct relation between the incidence of enlargement and the severity of the anaemia. This is in agreement with previous observations and the influence of other factors has been suggested (Ellis and Faulkner, 1939, Tung, Bien, Ch'u, and Wang, 1937), specially the age of the patient, the nature of the anaemia, and the amount of work done by the patient in the anaemic state. It has not been possible here to establish the importance of any of these factors, on the contrary the similarity of the findings in the enlarged and normal groups was close. The duration of anaemia is always difficult to determine, but it may be important, for the largest heart was found in a woman of 56 years with a history of 20 years' liability to bleeding from haemorrhagic telangiectasis. In contrast, the smallest heart observed was in a woman of 32 years with an even more severe refractory anaemia of nine years' duration, so that no definite conclusion is possible.

Regression in cardiac size was always accompanied by an improvement in the blood, but there was considerable variation in the haemoglobin level at which this took place, although a more constant figure might have been established if it had been possible to take more frequent films. It is nevertheless clear that regression usually occurred soon, often within two or three weeks of the beginning of treatment, and at a haemoglobin level substantially below normal. Furthermore, it was usually maximal in the first instance and only twice was any further change seen subsequently, even though the



improvement in the blood continued and the patients were re examined after intervals of nine to 15 months. The contrast between enlargement and murmurs in this respect has already been mentioned, and the details are presented in Table III.

*Heart failure.* Dyspnoea and oedema, cardiac enlargement, murmurs, and occasionally triple heart rhythm, suggest the presence of heart failure, but this explanation is not entirely satisfactory. Dyspnoea was often found without cardiac signs, while the absence of orthopnoea, and of clinical and radiological signs of pulmonary congestion show that it was not caused by heart failure. Oedema without other signs could not be of cardiac origin, and together with dyspnoea must be the result of other manifestations of anaemia, probably upon the peripheral capillaries and the respiratory centre. On the other hand cardiac enlargement, and a third heart sound, sometimes with T wave inversion of the lead CR<sub>1</sub> of the electrocardiogram, indicate preponderance of the right heart, and when accompanied by venous distension, hepatic engorgement, and oedema, suggest right heart failure. These signs were present in five cases, and in another there was venous distension and a third heart sound, but no cardiac or hepatic enlargement. Gross venous distension was observed in only two cases, but the cardiac signs in anaemia appear to represent varying degrees of preponderance and failure of the right heart.

### Discussion

Cardiac symptoms and signs are common in anaemia, but they are in some degree independent of one another, and are not directly related to the severity of the anaemia. Their frequency and resemblance to the stigmata of organic heart disease are not fully appreciated, for several of my cases were first seen in a Cardiac Department. Diagnosis can be difficult. Cardiac pain, sometimes accompanied by electrocardiographic changes which may be permanent, is not always easily distinguished from angina pectoris, while haemic murmurs, especially if diastolic or very loud, can be mistaken for signs of valvular disease. Cardiac enlargement may be considerable and permanent. The liability of anaemia to mimic cardiac failure should now be well known, but its role in the production of actual failure should not be overlooked. Finally it must be emphasized that it is on the recognition of anaemia and the results of treatment that a correct diagnosis depends.

The theories advanced to explain the changes described have been previously discussed, but further points emerge from my observations. The independence of the symptoms and signs of one another suggests that they are produced in different ways. Murmurs, if our present methods are valid, do not depend entirely upon enlargement, and experimental work (Lewis and Drury, 1923) justifies the belief that they are largely caused by a lowered blood viscosity. Myocardial anoxaemia may explain the fatty changes found *post mortem*, but my observations support the view that dilatation and hypertrophy which have also been reported cannot be explained in this way.

Regression in cardiac size after treatment tended to occur rapidly and to be maximal at once, even though the haemoglobin was still well below normal. This does not suggest a steady improvement in the nutrition of an anoxaemic muscle, and favours the explanation that enlargement is caused by a dynamic disorder of the circulation (Bouchut and Froment, 1934, Bouchut, Froment, and Bonnet, 1934, Fahr and Ronzone, 1922, Porter, 1937). Gross changes in the circulation have indeed been described, and their function is undoubtedly to compensate for the diminished oxygen carrying power of the blood. Several processes are involved including increased utilization of oxygen by the tissues (Liljestrand and Stenstrom, 1925, Nielsen, 1934, Richards and Strauss, 1928), but by far the most important is a greatly increased cardiac output. Sharpey-Schafer (1944) believes that this is mainly achieved by a raised venous pressure, and the observations recorded here support his view. The right heart would be overloaded and on the verge of failure and would be expected to show in varying degree the characteristic signs of venous distension, hepatic engorgement, triple rhythm, and electrocardiographic changes. Enlargement would be probable and might regress rapidly when improvement in the anaemia permitted the circulation to recover. In such circumstances cardiac pain depending on a disorder of the coronary circulation would be likely, and the well-known danger of blood transfusion in further overloading the circulation and causing acute heart failure would be understandable. The clinical picture resembles that seen in acute pulmonary embolism, and in some acute infections with circulatory failure, and the observations made suggest the possibilities of a new approach to the problem of failure in an apparently normal heart. The cause of the raised venous pressure is uncertain. Myocardial anoxaemia may play a part in the occasional production of permanent cardiac enlargement, where the hypertrophy which has been reported may be caused by the attempts of an abnormal myocardium to maintain a high cardiac output (Bouchut and Froment, 1939, Bouchut, Froment, and Bonnet, 1934). It may also be responsible for the more persistent electrocardiographic changes.

### *Summary*

1 Cardiac symptoms and signs, including cardiac pain, haemic murmurs, and enlargement, with occasional changes in the electrocardiogram, occur in anaemia, and usually disappear after treatment, but they sometimes persist. They are often difficult to distinguish from the signs of organic heart disease.

2 Enlargement of the heart in anaemia, accompanied as it sometimes is by a raised venous pressure, addition of the third heart sound, and inversion of the T wave in the right pectoral electrocardiogram, is an expression of right heart preponderance, which may progress to frank heart failure with hepatic engorgement and oedema. Dyspnoea and oedema can also be present as direct effects of the low haemoglobin content of the blood and not the outcome of heart failure.

3 The responsible mechanism may differ for the various signs and symptoms The probable factors are reviewed

I have to acknowledge the courtesy of the members of the Honorary Staff of the London Hospital in allowing me to study patients under their care I wish to thank Dr A A Cunningham and Dr. D Gutmann, of the Lister Emergency Hospital, Hitchin, for kindly allowing me to make use of their observations in one case

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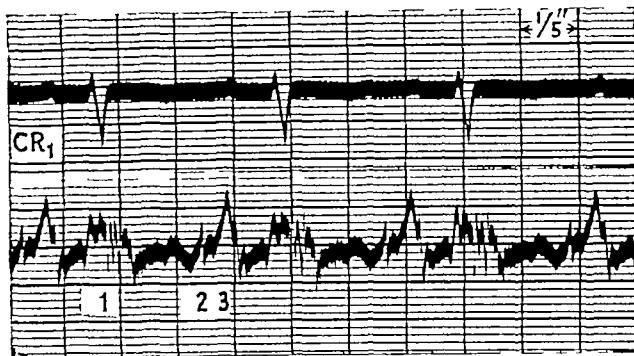


FIG 2 A woman aged 44 years Hypochromic anaemia Phonocardiogram to show third heart sound with T wave inversion in CR<sub>1</sub> of the electrocardiogram

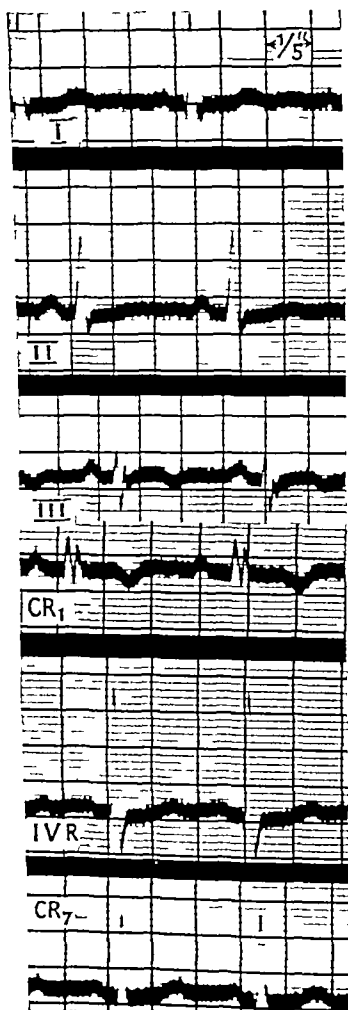


FIG 3(a) A woman aged 40 years Hypochromic anaemia Haemoglobin 39 per cent Flattening of T wave in lead II and inversion in leads III and CR<sub>1</sub>

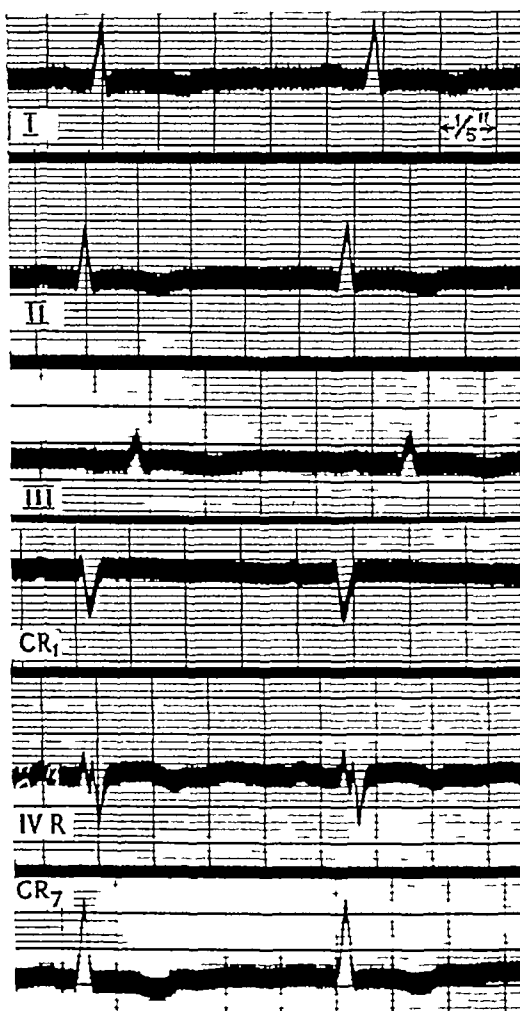


FIG 3(b) A woman aged 42 years Hypochromic anaemia Haemoglobin 50 per cent Inversion of T wave in leads I, II, III, IV(R) and CR<sub>1</sub>, and flat in CR<sub>1</sub>

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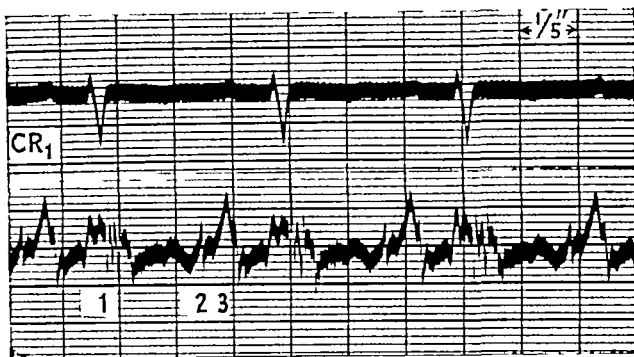


FIG 2 A woman aged 44 years Hypochromic anaemia Phonocardiogram to show third heart sound with T wave inversion in CR<sub>1</sub> of the electrocardiogram

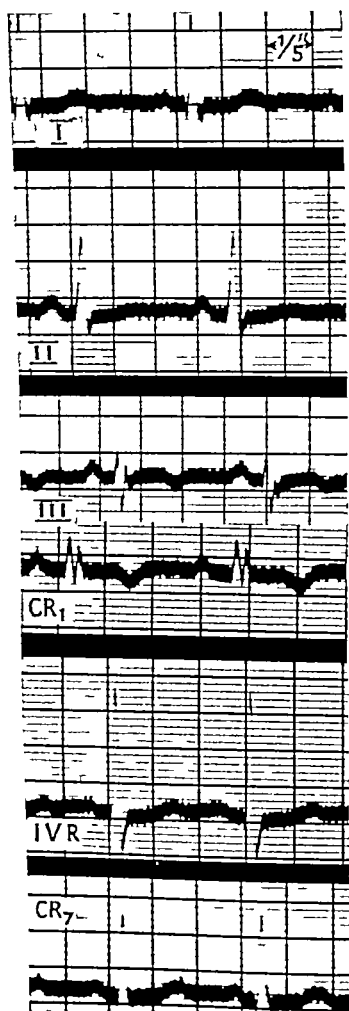


FIG 3 (a) A woman aged 40 years Hypochromic anaemia Haemoglobin 30 per cent Flattening of T wave in lead II and inversion in leads III and CR<sub>1</sub>

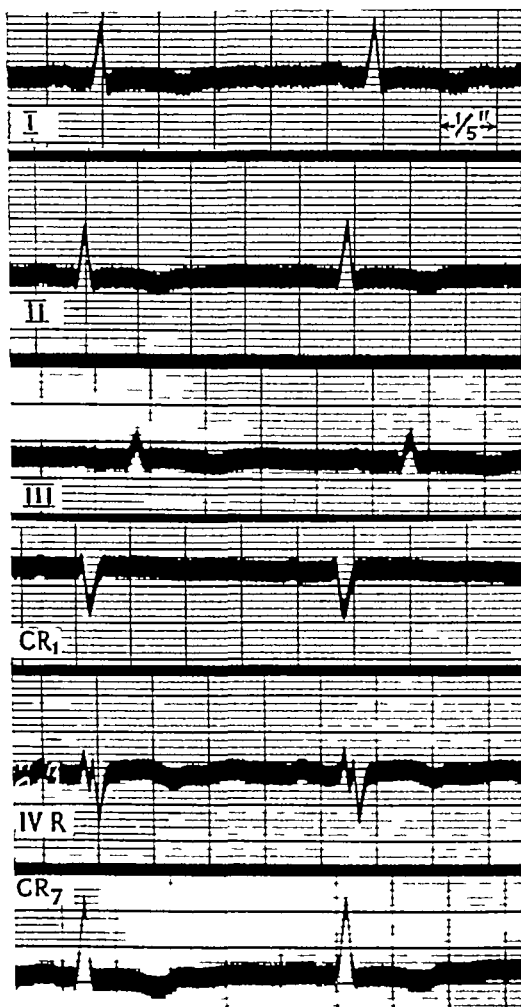


FIG 3 (b) A woman aged 42 years Hypochromic anaemia Haemoglobin 50 per cent Inversion of T wave in leads I, II, III IV(R) and CR-, and flat in CR<sub>1</sub>



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FIG 4 A woman, 48 years Hypochromic anaemia Reduction in heart size after treatment  
 Left 23 11 43 Haemoglobin 27 per cent Right 4 12 43 Haemoglobin 63 per cent





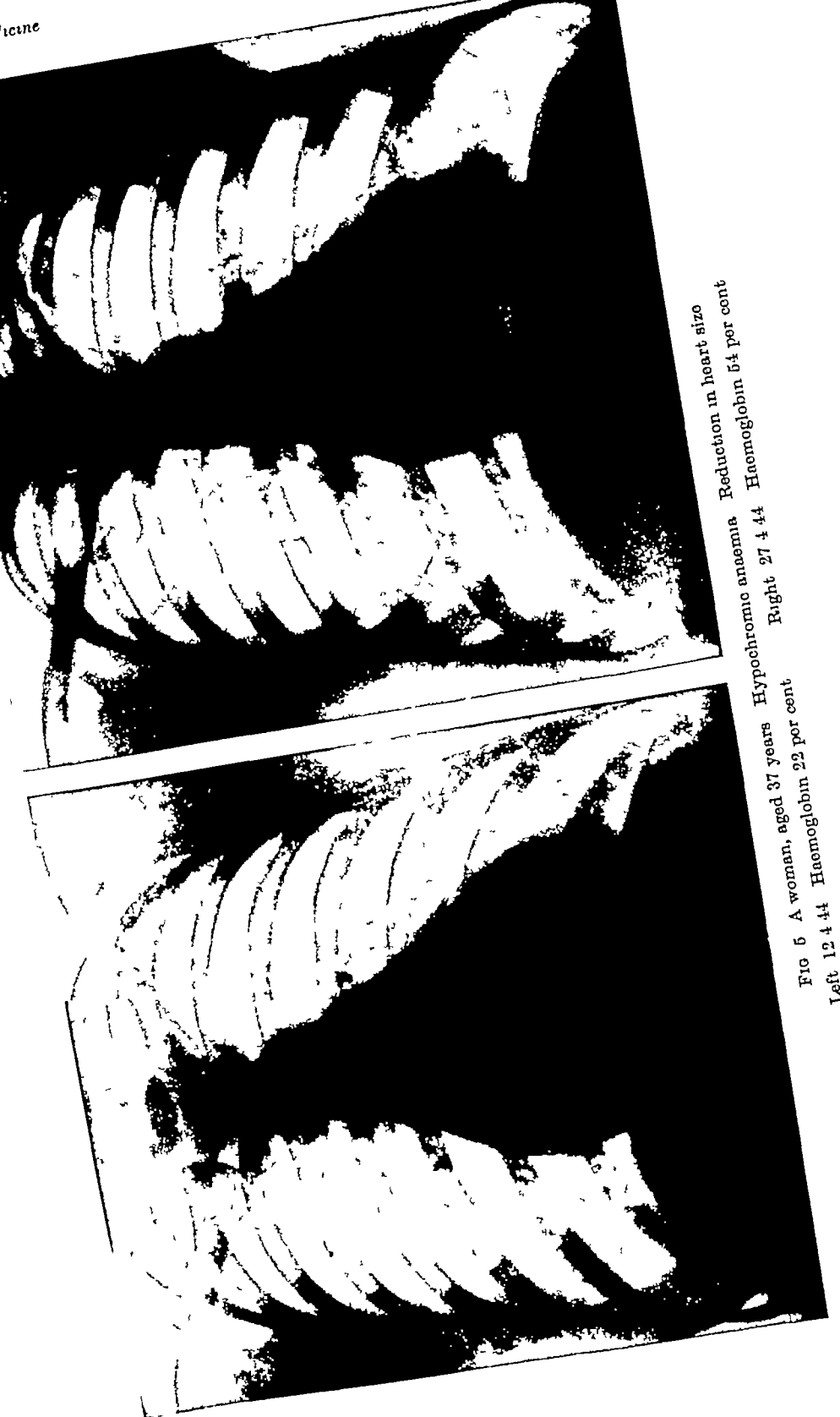


FIG 5 A woman, aged 37 years Hypochromic anaemia Reduction in heart size  
Left 12 4 44 Haemoglobin 22 per cent Right 27 4 44 Haemoglobin 54 per cent



COMPLETE CONGENITAL AGENESIS OF A LUNG<sup>1</sup>

By JOSEPH SMART

With Plates 10 and 11

CONGENITAL absence of an entire lung is a rare condition and has seldom been diagnosed in life. Two such cases are recorded in the present paper, in one of which there was also a congenitally small trachea. According to the literature the view generally expressed is that the single lung is emphysematous. Investigations carried out in these two cases do not support this belief, but rather suggest that true hypertrophy has occurred.

*Case Reports*

*Case 1* An unmarried woman, aged 30 years, was admitted to hospital on September 9, 1942 with dysmenorrhoea. She had suffered from asthma since childhood. Attacks of spasm might come on at any time, and were frequently caused by exertion. There was no allergic factor or any history of upper respiratory tract infection. On admission to hospital for dilatation and curettage of the uterus she developed an attack of asthma, and the question of her fitness for an anaesthetic was raised. On examination she was a small, thin woman with a normal temperature and pulse-rate, and physical examination was completely negative apart from the chest. This was symmetrically shaped and the movements were equal. On palpation the trachea was found to be grossly deviated to the right side and the cardiac impulse could not be defined. The vocal vibrations were equal on both sides anteriorly. The percussion note was resonant all over the front of the chest, and no area of cardiac dullness could be found. The breath sounds were vesicular with prolonged expiration on both sides, and rhonchi and sibilii were heard all over the chest. The cardiac impulse was found posteriorly just medial to the angle of the right scapula. Vocal vibrations were absent over this area, but otherwise the sounds were normal. The percussion note was resonant all over the left side and also over the right side, apart from a triangular area at the right base close to the spine, where the heart-beat could be felt. On auscultation the physical signs on the back were similar to those on the front of the chest. The heart-sounds could best be heard over the apex beat, and the dull area immediately medial to it, and they appeared quite normal in character. There was no clubbing of the fingers.

A postero-anterior X-ray (Plate 10, Fig 4) of the chest showed that the heart was situated on the right side, the trachea was deviated to the right, and there were some small opacities at the right apex situated around the displaced trachea, which suggested an old lipiodol injection. The lung tissue was visible on both sides and appeared normal. The ninth rib on the right

<sup>1</sup> Received August 29, 1945

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Q wave and an R which is slurred in its descent, T is inverted. Lead II is similar, but P is isoelectric, R is larger, and T is small but upright. Lead III is normal with upright P, normal R, no Q or S wave, and an upright T of moderate size.

A kymograph X-ray was taken which confirmed the earlier cardiological findings and showed that the shadow in the right side of the chest was the heart, but did not give any further information.

The question arose as to whether the left lung was emphysematous, or

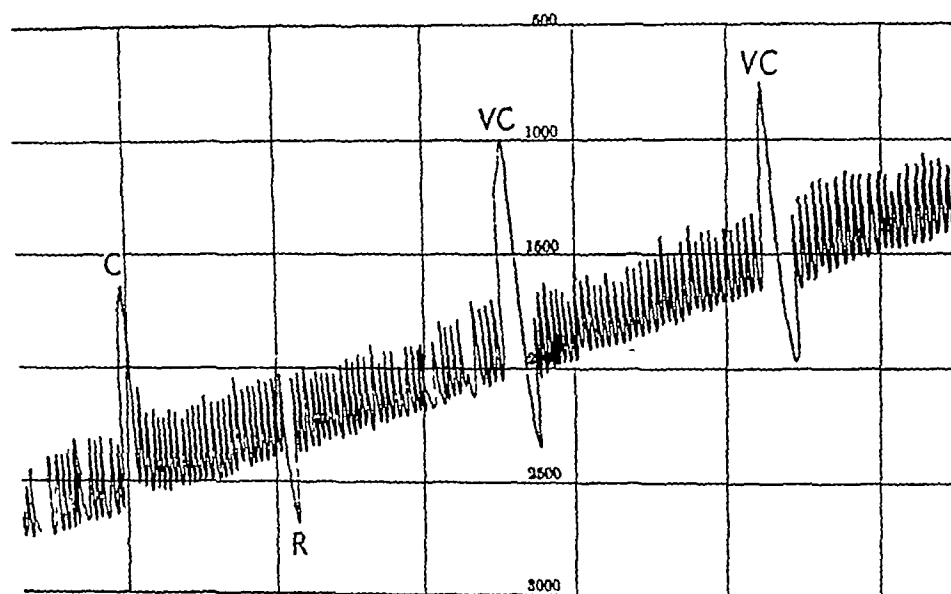


FIG 1 Case 1 Bronchspirometric tracing  
C = Complementary air R = Residual air  
VC = Vital capacity

whether it was hypertrophied. Christie and McIntosh (1934) have shown that this can be demonstrated by bronchspirometric tracings and by measurement of the intrapleural pressures. A bronchspirometric tracing was therefore recorded (Fig 1) and Professor Christie reported that it showed no evidence of emphysema. The vital capacity was 1,350 cc. A needle was inserted into the left side of the chest and the intrapleural pressure taken, the pressure was found to be  $-12$  to  $-5$  cm. of water on normal inspiration and  $-15$  to  $-5$  cm. on deep inspiration. Two days later the patient developed a severe asthmatic attack. The acute stage was relieved by adrenalin, but she continued to cough during the next two days and suddenly became extremely dyspnoeic. She was immediately admitted to hospital, and as there were signs of a pneumothorax, an X-ray was taken (Plate 11, Fig 8). This showed that the air extended to the right side of the chest, the lung edge being clearly visible on both sides, thus confirming the diagnosis. A needle was inserted into the pleural space and air withdrawn on two occasions, after which she made an uneventful recovery, and the



side showed a cystic swelling at its anterior end about  $1\frac{1}{2}$  in from the costochondral junction, the aetiology of which was obscure. It may have been a congenital deformity. In view of the gross abnormality disclosed by this examination, it was considered that further investigations should be carried out before the question of fitness for anaesthesia could be decided. In order to attempt to define the shape of the heart more accurately, X-rays were taken with greater penetration, and also a right lateral view (Plate 10, Fig 5). The first of these did not help at all with the diagnosis, the second showed the heart shadow to be situated posteriorly, and there was no cardiac shadow in the normal position. With the patient lying on her right side, lipiodol was then injected by the cricothyroid route. The postero-anterior X-ray (Plate 10, Fig 6) showed the bronchi of the left lung well filled, these were very slightly dilated and bronchi were also seen on the right side of the chest. The lateral film (Plate 10, Fig 7) was most remarkable, for it showed the left upper lobe bronchus coming off anteriorly, then dividing into its three main branches supplying both the right and left sides of the chest. On X-ray screen examination the left dome of the diaphragm could be seen situated rather low down and moving quite well, the right dome of the diaphragm was difficult to locate, but on screening in the right oblique position the anterior part could be seen at the same level as the left, but it did not appear to be moving. These findings suggested that the right lung was absent, but it was possible that there was a lung-bud representing the absent lung, and, in order to ascertain whether there was an opening into the trachea, bronchoscopy was carried out under local anaesthesia. The vocal cords were seen to be moving well and appeared normal, the trachea was normal in its upper part, but there was no evidence of any slit or opening to suggest a right bronchus. Some difficulty was experienced in passing the bronchoscope owing to the deviation of the trachea, but this was overcome, and the left upper lobe bronchus was then visible, coming off anteriorly, as was expected from the appearance of the lipiodol X-ray. Care was taken to exclude the possibility of a rudimentary bronchus at the level of the bifurcation of the trachea. In a normal adult woman the bronchoscope has to be passed approximately 8 in in order to reach the bifurcation of the trachea. No bronchus was seen at this level, and the first bronchus discovered was the left upper lobe bronchus coming off anteriorly. These findings proved the diagnosis beyond doubt.

Owing to the gross displacement of the heart it was considered necessary to have the opinion of a cardiologist. Dr John Parkinson saw her and reported as follows:

'On examination the pulse is 70 and regular. The cardiac impulse is felt medial to the lower angle of the right scapula and at the adjoining vertebral border. It is not unduly forcible and there is no thrill. The first and second sounds are normal, and there are no murmurs. The blood pressure is 110/75. There are no signs of cardiac failure. The electrocardiogram shows a regular rhythm at a rate of 90. In Lead I, P is slightly inverted, followed by a large

Q wave and an R which is slurred in its descent, T is inverted Lead II is similar, but P is isoelectric, R is larger, and T is small but upright Lead III is normal with upright P, normal R, no Q or S wave, and an upright T of moderate size'

A kymograph X-ray was taken which confirmed the earlier cardiological findings and showed that the shadow in the right side of the chest was the heart, but did not give any further information

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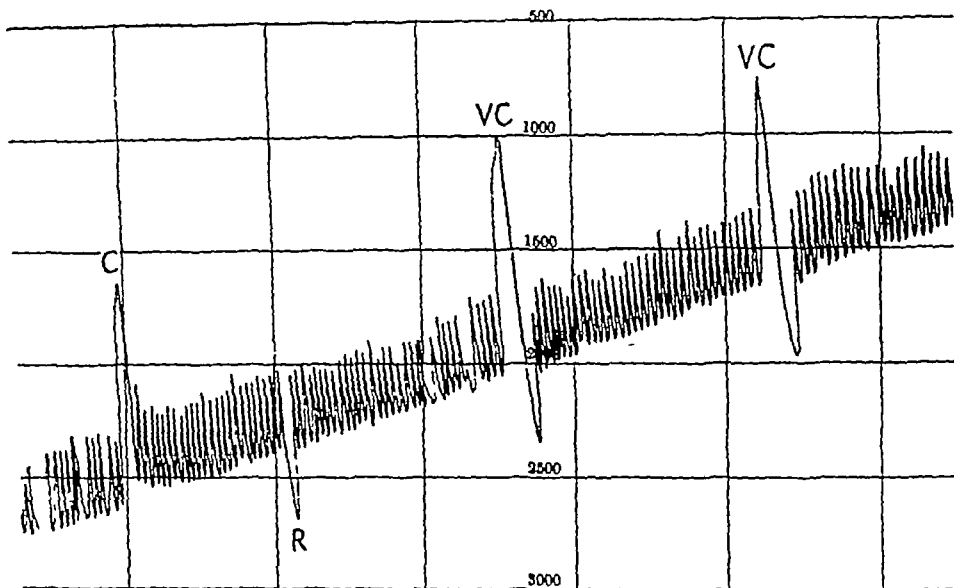


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lung had completely re-expanded within five days of her admission to hospital. It is possible that the lung was pricked while the pressures were being taken and sealed itself, but that the strain of the asthmatic attack and constant coughing had ruptured the previously weakened lung.

*Case 2* A married woman, aged 29 years, was seen at hospital on August 16, 1943, and gave a history of asthma. The attacks were not typical, but she complained of shortness of breath, specially on exertion, for as long as she could remember, and this symptom had been aggravated as a result of work in a factory. She also complained of pain in the praecordial area for the previous six months. It was not severe in character, but was more marked on exertion, at times it went down the left arm, and its relation to exercise was somewhat vague, since she had learned by experience to restrict her activities because of her dyspnoea. There was no allergic factor, no evidence of upper respiratory tract infection, and no abdominal disease to cause reflex spasm. In her past history she had had measles, whooping cough, and scarlet fever as a child. There was nothing relevant in the family history. On examination she was a healthy-looking, well-built woman, with stridor. The chest was symmetrical and moved equally. On palpation the trachea was found to be grossly displaced to the left, and the cardiac impulse to be in the mid-axillary line on the left side. Vocal vibrations were present on the right side and at the left apex anteriorly. The percussion note was resonant on the right side and impaired at the left apex. The area of cardiac dullness was displaced to the left. The breath sounds were vesicular on the right side and on the left side at the apex, and there were no added sounds. Posteriorly the chest moved equally, the percussion note was resonant on the right side, impaired at the left apex, and dull at the left base. The vocal vibrations were present on the right side, impaired at the left apex, and absent at the left base. The breath sounds were present on the right side, vesicular in character with prolonged expiration, and no added sounds were heard. On the left side the breath sounds were weaker, but present at the apex and absent at the base. There was no clubbing of the fingers. No other abnormality was discovered.

A postero-anterior X-ray of the chest (Plate 11, Fig 9) confirmed that the heart and trachea were grossly displaced to the left. The rib spacing was slightly less on the left than the right, the left dome of the diaphragm was obscured, and the right dome appeared normal. The lung markings on the right side were normal, and on the left some markings could be seen at the apex. A left lateral X-ray (Plate 11, Fig 10) showed the heart to be situated anteriorly, but no gross abnormality was detected. With the patient lying on her left side, lipiodol was injected by the cricothyroid route. A postero-anterior X-ray (Plate 11, Fig 11) showed that the trachea was much diminished in size and displaced to the left, there was no bifurcation of the trachea into the right and left main bronchi at the normal level, and the right upper lobe bronchus could be seen supplying the lung tissue on the left and right sides. The lateral X-ray showed the bronchi in the lung tissue, but it did not help materially in defining the exact distribution. Later, bronchoscopy was performed under local anaesthesia in order to ascertain whether there was any opening representing the left main bronchus,

and in view of the size of the trachea an infant's bronchoscope was used. The cords were seen to be moving well and appeared normal, and the upper part of the trachea appeared normal apart from its small size. Unfortunately it was impossible to pass even this bronchoscope more than two or three inches because of the size of the trachea, and it could not be passed a sufficient distance to ascertain whether there was any rudimentary opening present. Further X-rays were taken with barium, and the postero-anterior view showed gross displacement of the oesophagus to the left, this was confirmed

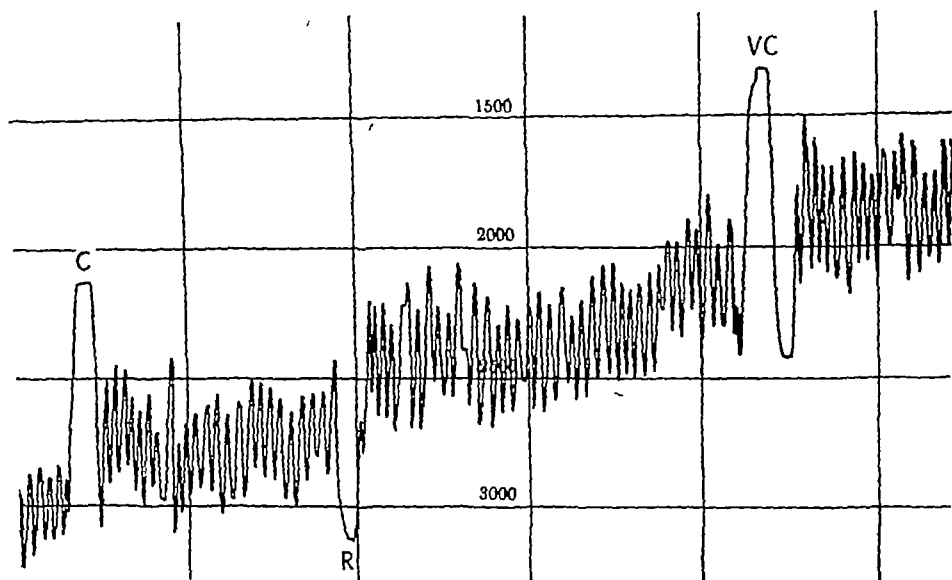


FIG 2 Case 2 Bronchspirometric tracing  
C = Complementary air R = Residual air  
VC = Vital capacity

in the left oblique view. At the same time the opening into the stomach was centrally situated and the gas bubble in it defined the level of the left dome of the diaphragm as a little above that of the right. On screening, the left dome was seen to be moving very slightly.

This case also was seen by Dr Parkinson, who reported as follows:

'On examination the patient is well-nourished and slightly breathless. No definite apex beat is felt, but there is pulsation about the left anterior axillary line. The heart sounds are normal and there are no murmurs. The blood pressure is 110/76. The electrocardiogram shows a normal rhythm with large S in Lead I, a bifid P and diphasic T in Lead II, and diphasic P, large Q and inverted T in Lead III. The pain is situated above the left breast and sometimes extends into the left arm. It appears while she is walking and never at rest. If present, and she does rest, it goes off in a few minutes. This is what I would call cardiac pain, but not angina pectoris.'

In order to correlate the findings in Case 2 with those in Case 1, the intra-pleural pressure on the right side was taken and was normal, being -12 to -6

om of water There were no untoward effects The bronchspirometric tracing was also taken (Fig 2) and Professor Christie expressed the opinion that it showed no evidence of emphysema The vital capacity was 1,150 c c For comparison a tracing from an emphysematous patient is shown in Fig 3

Case 2 patient was without doubt a case of agenesis of the left lung, together with a congenitally small trachea The asthma was due to stridor and not spasm of the bronchi The cardiac pain is difficult to explain, but it may have been due to anoxaemia associated with the smallness of the

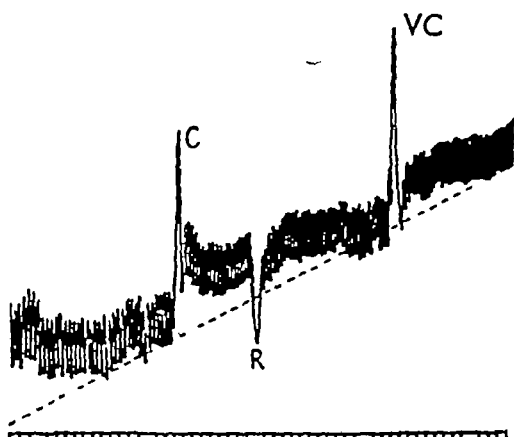


FIG 3 Bronchspirometric tracing of emphysematous patient, for comparison with Figs 1 and 2

C = Complementary air R = Residual air  
VC = Vital capacity

trachea Angiocardiography was contemplated in these two cases in order to demonstrate the presence or absence of the pulmonary arteries, but facilities were not available in this country

### Diagnosis

The diagnosis of this unusual condition is not difficult provided its possibility is borne in mind There are three cardinal clinical features, a symmetrical chest with equal or approximately equal movements, gross displacement of the trachea to one side, and displacement and rotation of the contents of the mediastinum The breath sounds are usually audible over the whole chest Further investigations which will prove the diagnosis are X-rays of the chest, lipiodol X-rays of the bronchi, and bronchoscopy Seventeen cases in which agenesis of one lung has been diagnosed in life are recorded in the literature, the diagnosis having been confirmed by autopsy on five occasions The post-mortem findings in three cases (Paul, 1928, Ratjen, 1867, Schuchardt, 1885) suggest congenital atelectasis with bronchiectasis, but in each case the chest was symmetrical and had equal movements Neisser (1901) reported similar cases and suggested congenital atelectasis with bronchiectasis, but this was not confirmed *post mortem* Inaccurate diagnoses were probably

due to the rarity of the condition, and to the fact that most of the cases occurred before lipiodol was in use or the bronchoscope available. It appears that only 10 of the previously reported cases were examined by bronchoscopy. Errors of diagnosis usually occur through lack of observation of one of the clinical features, for example, symmetrical movements of the lung. Fibrosis of the lung or massive collapse of the lung appear to have been the most common alternative diagnoses. In fibrosis of a lung after infection there is invariably lack of movement of the affected side, together with displacement of the trachea and mediastinum, but without rotation of the mediastinum, while in massive collapse there is lack of movement and displacement without rotation, usually associated with a considerable degree of respiratory embarrassment, and absent breath sounds on the affected side. With the improved technique of lipiodol injection into the bronchi and bronchoscopy, the diagnosis can be proved. Both these investigations can be carried out without risk to the patient.

#### *Analysis of Reported Cases*

There are 104 cases of congenital aplasia of the lungs published in the literature, and two further cases are reported in the present paper. Seventy-five cases appear to have been correctly diagnosed and 29 incorrectly diagnosed. The physical signs reported in 21 of the cases suggest gross fibrosis or congenital atelectasis of the lung rather than an absent lung, because there was marked deformity and loss of movement on the affected side. The names of the authors are given in the References, Section A. In three cases (Paul, 1928, Rohmer and Borchert, 1897, Schuchardt, 1885) post-mortem examinations were performed and the findings confirmed congenital atelectasis of one lung. A further eight of the recorded cases suggest an alternative diagnosis. Tackius (1702) reported a case which appears to have been one of advanced pulmonary tuberculosis, in which one lung was completely destroyed and there was evidence of this disease in the other lung. Paul (1928) reported a case of congenital absence of both lungs, and a case in which an abnormal branch of the aorta leading to the left lung is described, but no reference is made to the lung, so that this cannot be considered as a case of complete congenital absence of a lung. Allen and Affelbach (1925) and Schmit (1893) both reported a case of complete congenital absence of both lungs. Pruys, Veen, and Zuidema (1939) described a patient in an article entitled 'Agenesis of the Lung' who appears to have had a cystic lung. Bell (1893) reported two cases of agenesis of the lung, the diagnosis of one apparently being correct, but the second case was probably due to a traumatic lesion, followed by suppuration and destruction of the lung. Finally, Gartside (1943) described a case in which the physical signs and bronchogram suggest bronchial stenosis. Further reference to congenital absence of a lung is made by 12 other writers. They do not describe actual cases, but only review the literature. These authors are listed in the References, Section B.

It appears, therefore, that 75 cases of true congenital absence of one lung have previously been described. The names of the authors are given in the References, Section C. In two of the cases reported (Lukin, 1885, Rivière, cited by Furst, 1878) the original papers were not available. In only 17 of the cases was the diagnosis made during life, and in five it was confirmed by autopsy. In 44 of the 75 cases the left lung was absent, and in 28 the right, in three cases there was no mention as to which side was missing. Complete absence of a lung occurred in 33 cases, 18 times on the left side and 15 on the right. A rudimentary lung or bronchus was present in 35 cases, 23 times on the left side and 12 on the right, in the remaining seven cases no accurate record was made as to the presence or absence of a rudimentary lung.

*Sex.* The condition has been reported 27 times in male subjects, 14 on the left side and 13 on the right, and 35 times in female subjects, 23 times on the left side and 12 on the right. In the remaining 13 cases the sex was not mentioned.

*Age distribution.* Thirty-five of the recorded cases have been under the age of 1 year. Twenty-three have been described in patients between the age of 1 and 30 years and eight cases in patients between 31 and 72 years. In nine cases the age was not mentioned. The youngest recorded case was a miscarriage at seven months, which lived for two hours, the oldest was a woman of 72 years, who died of a cerebral haemorrhage. It seems that, provided a person with this condition survives the first year of life, death does not necessarily occur because of the pulmonary abnormality. This view is confirmed by the analysis of the 31 cases over the age of 1 year. Of these, five died of pneumonia, 10 died from non-pulmonary conditions, and nine of the patients were alive when described. In seven cases the cause of death was not reported.

*Frequency of occurrence.* The condition is very rare, and it is difficult to estimate the frequency of its occurrence. Ellis (1917) reported two cases in 30,000 autopsies, but clearly this figure is of no statistical value.

#### *The Evolutionary Development of the Lungs*

The exact way in which the lungs develop is obscure, but there are three main theories, the reduction theory (Aby, 1878, D'Hardiviller, 1896, 1897, Bremer, 1904), the extension and migration theories (Willach, 1888, Young and Robinson, 1889, Ewart, 1889, Zumstein, 1889, Narath, 1892, Huntington, 1898, Blisnianskuja, 1904), and the selection theory (Huntington, 1920).

The reduction theory works from the assumption that in the evolutionary history of the mammalian lung the organ possessed a bilaterally symmetrical ground plan. Aby (1878) discussed at length the presence of the eparterial bronchus on the right side and suggested that the lack of symmetry is due to the suppression of the eparterial component on the left side. This theory assumes a bilateral ground plan and therefore does not cover the earliest stages of the development of the lung.

The extension theory also assumes a bilaterally symmetrical bronchial tree, with the same number of bronchi on each side, and suggests that progressive unfolding of the respiratory area is possible, specially in the cephalic sectors, and that this is in response to increase in the functional demand. The right eparterial bronchus rises in response to this demand. As in the previous theory, the presence of a bilaterally symmetrical bronchial tree is assumed, and so this theory does not help in deciding the aetiology of agenesis of a lung. The migration theory also assumes a bilaterally symmetrical bronchial tree with a fixed number of bronchial derivatives. The roots of these branches under the stimulus of progressive evolution are capable of migrating from their original site.

The selection theory was advanced by Huntington (1920). In the initial stage of development of the lungs of pulmonate vertebrates the primitive lung is derived from the ventral wall of the foregut, lined with epithelium continuous with that of the intestinal canal (endoderm). This is surrounded by the splanchnopleuric mesoderm of the pulmonary blastema. The primitive lung is formed from two components, conductory (endodermal) and respiratory (mesodermal). The circumference of the extending endodermal lung sac develops points of increased epithelial proliferation. These areas of heightened mitotic activity protrude as hollow epithelial buds whose lumina communicate with the central cavity of the lung sac. As the surface area of the lung sac increases, the previous uniform budding of the pulmonary vesicles is replaced by a smaller number of localized areas of more intensive proliferation which develop into sac-like protrusions. Each of these protrusions repeats in detail the structure of the primitive lung sac, and the walls of the adjacent chambers come into contact with the mesodermal vacuoles and fuse. Thus, according to Huntington (1920) the lungs develop simultaneously from the primitive gut centrally and from a number of points representing the intrapulmonary system peripherally. The meeting points of the conducting and respiratory components of the adult lung lie within the intermediate area of the respiratory bronchus, effecting a gradual transition between the conducting tube and the alveolus.

These theories deal with the evolutionary development of the mammalian lung, which is an obscure subject, as is the exact development of the human lung. None of the theories explains the congenital absence of one lung, but the selection theory would account for the phenomenon. If the conducting component (organizer) fails to bifurcate through some endogenous error it is conceivable that the portions of lung (mesodermal) arising from the respiratory component on each side would join to form one single lung. This would account for the fact that the lung is hypertrophied and not emphysematous, since morphologically it may represent both lungs. This suggestion is purely hypothetical, and evidence that hypertrophy occurs in one lung when the other is absent is no proof of this view.

Various other theories have been put forward to account for the absence of one lung. Eppinger (1896) suggested that enlargement and displacement



of the thymus may be the cause Klebs (1874) has suggested that the excessive tension of the amnion when the embryo rotates may prevent development of one lung Schwabe (cited by Schneider, 1912) suggested an endogenous error in development due to some alteration in the germ plasm Tichomiroff (1895) suggested that early intrathoracic disturbances of pressure or infection might be the cause

Schneider (1912) has distinguished three grades of hypoplasia of the lung Bronchopulmonary agenesis, in which there is no evidence at all of the absent lung

Aplasia of the lung with a bronchial rudiment, in which there is a minute bronchus or the remains of a bronchus the end of which is surrounded by a small amount of pulmonary tissue about the size of a cherry and completely airless

Hypoplasia gravissima, in which there is poor development of the main bronchus which fuses into a small mass of pulmonary tissue, the bronchi are frequently dilated in this mass of tissue and the alveoli are usually atelectatic

Castellanos and Pereiras (1942) have classified hypoplasia of the lung into five groups based on the assumption that the lungs develop from a pulmonary portion and a bronchial portion

Bronchopulmonary aplasia, which corresponds to Schneider's aplasia of the lung

Bronchial hypoplasia with pulmonary aplasia, that is, there is a small rudimentary bronchus but no pulmonary tissue

Bronchopulmonary hypoplasia, that is, a small bronchus joined to a minute amount of pulmonary tissue This group and the one which precedes it appear to correspond with Schneider's second group

Bronchial hypoplasia with pulmonary aplasia, in which there are small semidilated bronchi without pulmonary tissue

Congenital bronchoectasia with alveolar aplasia in which there are dilated bronchi in a very small lung, with some fibres around them, but no evidence of alveoli tissue in the lung This group and the one which precedes it appear to correspond with Schneider's third group

The views of Castellanos and Pereiras (1942) are complicated and there does not appear to be sufficient histological evidence in the literature to support them It appears that Schneider's (1912) classifications of bronchopulmonary aplasia, and aplasia of the lung with a bronchial rudiment, are correct and can be substantiated histologically, but from the histological sections it is more probable that the cases described as hypoplasia gravissima are actually cases of congenital atelectasis of one lung This view is supported by the post-mortem findings in the cases described by Paul (1928, Case 2), Rohmer and Borchert (1897), and Wollmann (1891)

#### *The Structure of the Existing Lung*

Attention has been concentrated upon the missing structure rather than upon the existing lung In 57 post-mortem examinations the histology of the

existing lung is recorded in only seven cases. No histological evidence is given in the others, but many writers mention that it is large, of whom Berliner (1909), Gross (1905), Jarisch (1919), Knott (1934), Ratjen (1867), and Tom (1934) describe the existing lung as emphysematous macroscopically. Von Graff (1905) described the macroscopical appearances of a foetus in which the right lung was absent and the left considerably enlarged. He drew attention to the fact that this enlargement cannot be due to functional hypertrophy, because the lungs are not used *in utero*. In the post-mortem cases in which the histology of the existing lung is mentioned, Dyson (1934) reported areas of emphysema and infection. Finner (1932) reported that microscopically the enlarged lung was normal. Gross (1905) stated that there was evidence of emphysema, but that the existing lung was grossly abnormal, having no lobar subdivisions. Killingsworth and Hibbs (1939) reported that the existing lung showed emphysema in the upper lobe with occasional areas of focal atelectasis. The lower lobe showed foetal atelectasis. The emphysematous changes were probably associated with the congenital atelectasis of the lower lobe. Oberwarth (1904) stated that hepatization was present, but that the lung otherwise appeared normal, the infant died from pneumonia. Welsch (1928) recorded that there was microscopical evidence of hypertrophy. Rienhoff (1936) recorded a case in which the microscopical appearances of the enlarged lung were found to be normal.

The investigations in my two cases favour the view that hypertrophy has occurred. In each case the one lung present filled the whole of the thoracic cage, and it is clear that its volume was considerably larger than that of a normal lung. The enlarged lung must be either emphysematous or hypertrophied in order to fill up the chest space. Histological evidence is the only certain method of showing that hypertrophy has occurred, but Christie and McIntosh (1934) have shown that the presence of emphysema can be demonstrated by the loss of elasticity that occurs in an emphysematous lung. He has shown that the intrapleural pressure in emphysema is markedly reduced, and that this loss of elasticity can also be demonstrated by taking vital capacity tracings on a recording spirometer. The normal subject, after taking a deep breath, will expire all the air and return at once to his previous respiratory volume, whereas in a case of emphysema the lung is already over-stretched and fails to expel all the air inspired, so that the tracing does not return to its previous level for several respiratory cycles. The intrapleural pressure in each of the cases reported was normal, and the bronchspirometric tracings show that all the air was expired and the tracing returned to its previous level without delay. These findings show that in neither of my cases was there any evidence of emphysema. In view of the size of the lung it is assumed, therefore, that hypertrophy must have occurred.

#### *Other Congenital Abnormalities*

A further abnormality which occurs in association with aplasia of the lung is the absence of pulmonary vessels on the affected side, this abnormality

is invariably found in true aplasia of the lung Castellanos and Peréiras (1942) have demonstrated this during life by angiocardiology Other congenital abnormalities may occur with the condition In the case of Botar and Orts (1932) there was an ectopic left kidney, a unicornuate right uterus, an abnormally shaped skull, and hyperplasia of the left adrenal Chilaiddi (1910) and von Graff (1905) reported atresia of the anus In the case described by Gross (1905) there was underdevelopment of the left side of the face, and of the auricular appendages, together with a stricture of the anus, which was anteriorly displaced In one of the cases described by Paul (1928) there was absence of the left radius and metacarpals and of the basal phalanx of the thumb The oesophagus ended blindly just below the level of the trachea

### Summary

- 1 Two cases of agenesis of a lung diagnosed in life are described, one of the right, the other of the left lung
- 2 The diagnostic features are a symmetrical chest with equal movements, together with gross displacement and rotation of the mediastinum
- 3 A review of the literature is given
- 4 The theories of the development of the lung are discussed
5. Records of intrapleural pressures of the existing lung, and broncho-spirometric tracings, suggest that in each case the lung was hypertrophied rather than emphysematous
- 6 No cardiac abnormality beyond displacement was noted
- 7 Other congenital abnormalities are common

I wish to thank Professor R. V. Christie and Dr John Parkinson for their help and interest in these cases

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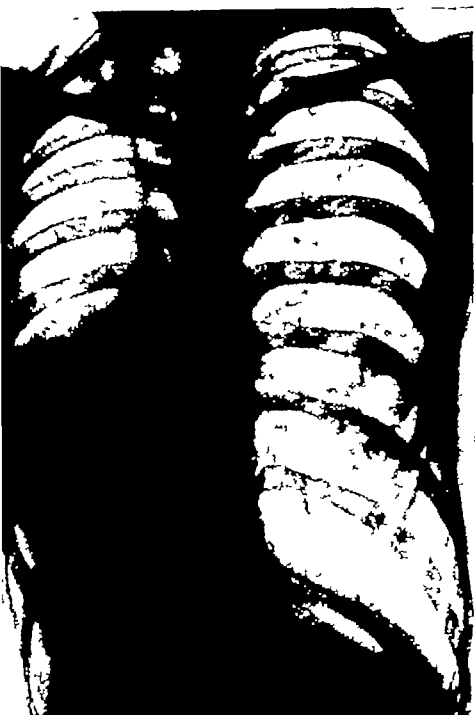


FIG 4 Case 1 Postero anterior X ray of chest to show absence of right lung



FIG 5 Case 1 Right lateral X ray of chest Barium has just been swallowed



R

FIG 6 Case 1 Postero anterior bronchogram



FIG 7 Case 1 Right lateral bronchogram





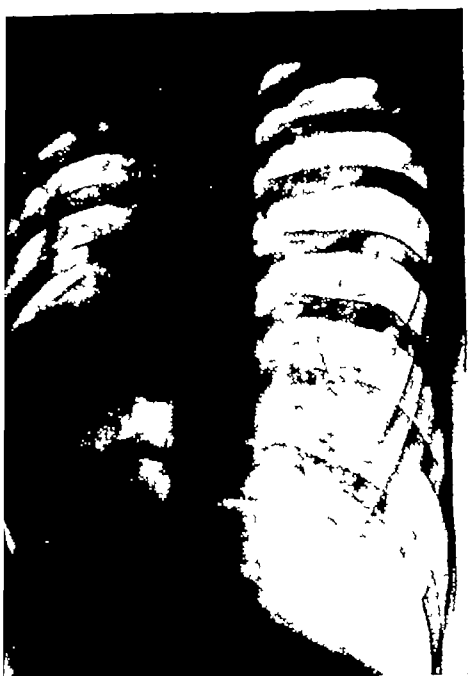


FIG 8 Case 1 Postero anterior X ray of chest, showing pneumothorax. Note that air can be seen on both sides

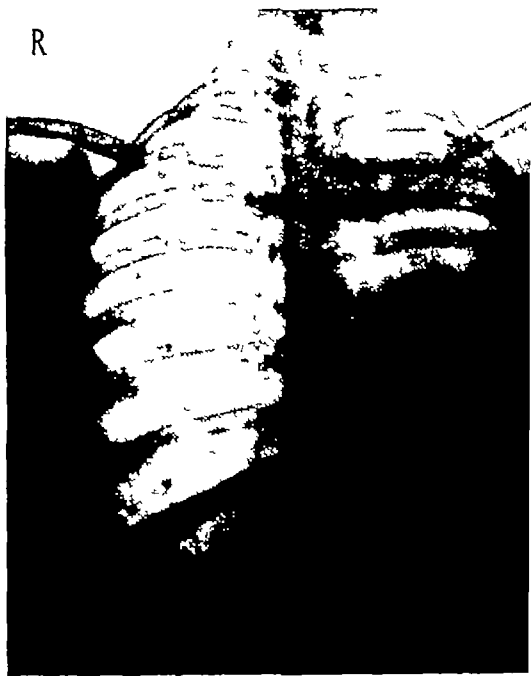


FIG 9 Case 2 Postero anterior X ray of chest to show absence of left lung



FIG 10 Case 2 Left lateral X ray of chest

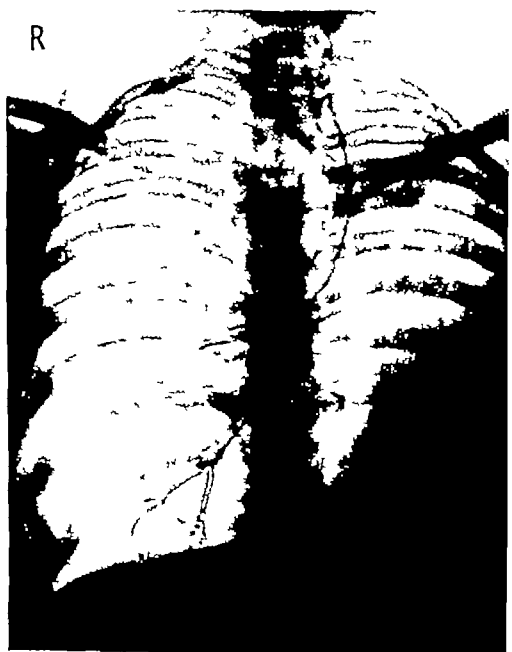


FIG 11 Case 2 Postero anterior bronchogram



ANOMALIES OF INTESTINAL ABSORPTION OF FAT<sup>1</sup>

## 1 THE DETERMINATION AND SIGNIFICANCE OF FAECAL FAT

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*Introduction*

Two main theories have been put forward to explain the normal absorption of fat from the intestine. The lipolytic hypothesis (Verzár and McDougall, 1936) suggests that fat must be completely hydrolysed and that the resultant fatty acid passes into the cells in combination with bile salts. In the cell triglyceride is resynthesized after phosphorylation under the control of the adrenal cortex. The re-formed fat passes entirely by the thoracic duct into the systemic circulation. The partition hypothesis (Frazer, 1938) suggests that fat is only partly hydrolysed. The unhydrolysed portion is finely emulsified by a monoglyceride/bile salt/fatty acid complex (Frazer, Schulman, and Stewart, 1944, Frazer and Sammons, 1945), and enters the intestinal cell as a finely dispersed emulsion. Some of the fat is also absorbed as fatty acid. The unhydrolysed fraction passes mainly by the thoracic duct to the systemic circulation and the fat depots, whereas most of the fatty acid passes direct to the liver via the portal vein (Frazer, 1943 *a, b*). Phosphorylation may play a part in the modification of the interfacial film of the unhydrolysed fat globules (Elkes and Frazer, 1943). The effect of the adrenal cortex is possibly secondary to its influence on electrolyte metabolism. In view of the differing explanations of the normal processes, it is not surprising that the pathology of anomalous fat absorption remains obscure. The object of the present investigation was the study of the various conditions in which fat absorption appears to be abnormal, in order to elucidate, if possible, the underlying pathological faults, and to correlate these observations with the normal mechanism of intestinal absorption of fat. The present paper is concerned only with the determination and significance of fat in the faeces with special reference to the development of the best methods of study, the determination of the criteria for assessing abnormality, and the interpretation of the analytical data.

*Methods*

*Diet* A standard diet containing 50 gm of fat, 250 gm of carbohydrate, and 75 gm of protein was used. The food equivalents were calculated from

<sup>1</sup> Received November 8, 1945



Concentration in the presence of a little alcohol was sometimes necessary to complete drying, which took about 30 min. The dry residue was extracted three times with 5 to 10 c.c. of petroleum (40° to 60° C fraction) and filtered into a weighed 50 c.c. bolt-head flask. After removal of the solvent, the total fat and triglyceride/fatty acid fractions were weighed. The weight of extracted fat was usually of the order of 100 mg. The fatty acid was determined by titration in benzene with alcoholic caustic soda solution.

*Selection of patients* Three groups of patients (41 in all) were used as controls. In the first group of 15 cases the only criterion for inclusion was the presence of diarrhoea, in three cases charcoal given as an indicator appeared in less than seven hours. In none was there any other evidence, either clinical or metabolic, of steatorrhoea. The diagnoses included ulcerative colitis, amoebic dysentery, gastro-enteritis, and chronic anxiety states. The second group of 12 cases was under treatment for anaemia, six patients had pernicious anaemia, three cirrhosis of liver and macrocytic anaemia, two iron deficiency anaemia, and the remaining patient had a macrocytic hyperchromic anaemia of unknown aetiology. One patient with pernicious anaemia and diarrhoea showed only 90 per cent absorption, but two further balances over longer periods showed 94 and 97 per cent absorption. The third group of 14 cases consisted of hospital patients chosen at random, usually those admitted for gastro-intestinal investigations in which steatorrhoea was not suspected.

In 79 other patients an excess of faecal fat might have been expected or was demonstrated. These may be grouped as follows.

*Idiopathic steatorrhoea* (29 cases) The diagnosis in these cases was based, after excluding possible alternatives, on the presence of a characteristic haematological and abnormal electrolyte picture, flat glucose tolerance and chylomicrograph curves, low fasting serum-lipoids, and a suggestive history. If the fat balance test introduced an element of doubt, the test was repeated. In Case 54 the history dating back to childhood and the clinical and laboratory findings were sufficient to justify the diagnosis. Duodenal intubation was not carried out on any of these cases, so that the possibility of fibrous pancreatitis was not ruled out.

*Tropical sprue* (21 cases) Five of these cases were seen in relapse, and had been under treatment for three to 10 years. Eight had been diagnosed in India on account of anaemia, glossitis, and diarrhoea with high percentage of faecal fat, but when seen in this country had apparently made a complete recovery. The remaining eight cases, similarly diagnosed in India, still had some fat intolerance and minor biochemical changes.

*Pancreatitis* (7 cases) The diagnosis in five cases was confirmed by autopsy or operation. Two cases, one a diabetic with recurrent pale loose stools, and the other a patient with severe bronchiectasis and previous admission to hospital for coeliac disease, have also been placed in this group.

*Lacteal obstruction* (2 cases) Case 105 had extensive 'chyladenectasis', first diagnosed at operation and later confirmed at autopsy. Case 106 had

standard food tables (McCance and Widdowson, 1940) and checked from time to time by analysis of a 24-hour ration. The error in fat content did not exceed four per cent. The patient was placed on this diet for at least 48 hours prior to the commencement of the test, to ensure that the patient was in balance. The use of a 50 gm fat intake as the standard, while well tolerated by patients with steatorrhoea, has certain disadvantages. Errors in either ingestion or collection and estimation of faecal residues cause a greater variation in the calculation of percentage absorption than when the diets contain more fat. The production of a palatable fat-free diet is difficult, and it seems likely that many diets reported as such in the literature may contain as much as 40 gm of fat per diem. In a few cases we used diets containing 20 gm of fat, but they were unsatisfactory as they were unappetizing and were not tolerated for long.

*Collection of specimens* Two methods were used in collecting specimens. In the first, three capsules of carmine (0.9 gm) were given on an empty stomach at 7 a.m. on the first day of the test, and at the same hour two, three, or four days later charcoal (2 oz.) in water was given. Stools were examined as passed and saved as soon as the carmine appeared. The first stool containing charcoal was discarded, and the collection thus completed. The second method (Rekers, Pack, and Rhoads, 1943) entailed the administration of 500 c.c. of normal saline as an enema after the evening meal. The result was discarded. A second saline enema was given two, three, or four days later at the same hour. The results of this, together with the stools passed after the first enema, completed the collection. We have used both methods, but are now using the second in the majority of our cases. This proved the more convenient, since markers are often difficult to detect and may interfere with the subsequent examination of the specimen in the laboratory. The results in the two methods did not show any significant difference. The period of collection was, with fluid or semifluid faeces, 48 hours and, in the case of patients with normal or constipated stools, 72 or 96 hours.

*Methods of analysis* Five-sixths of the determinations have been made by Cammidge's (1913) modification of the Schmidt-Werner method. The remainder have been carried out by a wet extraction method.

*Estimation of faecal fat by wet extraction method* The faeces were transferred to a glass jar with distilled water and mechanically stirred until homogenized. Water was added until a thick cream was produced, usually about 700 c.c. was required for a 48 hr specimen. The total volume was measured. Two 20 c.c. aliquot portions were taken and each poured through a funnel with a long outlet tube to the bottom of a continuous ether extraction apparatus. The faecal matter was washed in with a minimal quantity of water, and 20 c.c. of 95 per cent alcohol added to each portion. To one, 2 c.c. of concentrated hydrochloric acid was also added. Extraction was continued until the supernatant layer of ether was colourless even after adding a little more 95 per cent alcohol. This usually took 1 to 1½ hr. When complete, the ether and alcohol were removed under reduced pressure at 50° to 60° C.

Concentration in the presence of a little alcohol was sometimes necessary to complete drying, which took about 30 min. The dry residue was extracted three times with 5 to 10 c c of petroleum (40° to 60° C fraction) and filtered into a weighed 50 c c bolt-head flask. After removal of the solvent, the total fat and triglyceride/fatty acid fractions were weighed. The weight of extracted fat was usually of the order of 100 mg. The fatty acid was determined by titration in benzene with alcoholic caustic soda solution.

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marked reticulo-endothelial proliferation and caseating tuberculous lesions in the mesenteric glands

**Surgical conditions (6 cases)** All diagnoses were confirmed by operation, and included gastrocolic fistulae, ileotransverse colostomies, and Crohn's disease with ileal resection

**Malnutrition (6 cases)** The occurrence of pale stools, fat intolerance, and similarity of the blood and radiological pictures to those found in steatorrhoea led to fat balance tests being carried out on six repatriated prisoners of war

**Miscellaneous group (8 cases)** Four of these cases had duodenal ulceration in addition to longstanding steatorrhoea. Though they had many symptoms and signs similar to those of idiopathic steatorrhoea, we have regarded them provisionally as cases of pancreatitis. In the remaining four cases the excessive loss of fat appeared to be the primary factor in their illnesses, though the cause of the steatorrhoea still remains obscure

### *Results*

The results of 160 observations in these 120 patients are summarized in Table I. More detailed findings of the patients with idiopathic steatorrhoea, tropical sprue, and pancreatitis are given in Tables III to V

**Malnutrition** Of the three cases on a 50 gm fat diet, two showed minor defects of absorption (84 and 87 per cent). The remaining three cases had all regained  $1\frac{1}{2}$  to 2 stone in weight at the time of examination, but still had a tendency to diarrhoea. The balance tests were carried out in an outside hospital on a constant low fat diet. Calculation of this diet showed, however, a maximum intake of 80 gm of fat daily, and on this basis the results (91, 91, and 93 per cent) must be regarded as within normal limits. In two other cases on a low fat diet the exact composition of which was not known, more than 18 gm of fat was excreted daily

**Macroscopical and microscopical appearances** The description given by Gee (1888) in his paper 'On the coeliac disease' has been frequently quoted, but it is so accurate for many cases that its repetition needs no apology. 'The signs of the disease are yielded by the faeces, being loose, not formed, but not watery, more bulky than the food taken would seem to account for, pale in colour, as if devoid of bile, yeasty, frothy—an appearance probably due to fermentation, stinking stench often very great, the food having undergone putrefaction rather than concoction. The pale loose stool looks very much like oatmeal porridge or gruel. The hue is somewhat more yellow, other-wise more drab. True the dejections are faecal, more liquid and larger than natural, but they are not always more frequent than natural, it may be that the patient voids daily but one large loose whitish stinking stool.' The use of the adjectives pale, yeasty, frothy, stinking has persisted, often to the exclusion of the remainder of Gee's description. The stools of many of our patients differed from this classical description, being of normal colour

and consistency, and in an appreciable number of cases of idiopathic steatorrhoea, the presence of abnormal fat content could be detected only by quantitative fat analyses. Stools were usually passed once or twice a day. Many of the proved cases of steatorrhoea had long periods of normal bowel habits, and, not infrequently, of constipation. Thus, Case 51, who had been under observation since childhood for coeliac disease, had no intestinal symptoms. She had, however, a refractory macrocytic anaemia, and recurrent severe mouth ulceration. Her faeces were dark and constipated. Fat balance tests showed only 82 per cent absorption.

Microscopical examination of the faeces of idiopathic steatorrhoea and tropical sprue usually show an excess of fatty acid crystals. Occasionally in severe diarrhoea muscle fibres may be seen, but usually no other abnormal constituents. Hurst (1942) considered that the microscopical features were so characteristic that quantitative estimation of the fat was unnecessary. While the presence of excess fatty acid frequently indicates steatorrhoea, we encountered a sufficient number of exceptions, both with and without fatty acid crystals, to make this qualitative method of diagnosis unreliable for our purpose.

### *Discussion*

The essential feature of our series of cases was the presence of an abnormal amount of fat in the faeces, and diarrhoea was not a constant symptom. Four main points may be considered, the quantitative criteria upon which the assessment of normality or otherwise is based, the significance of the percentage hydrolysis and composition of faecal fat, the relationship of intestinal hurry to malabsorption of fat, and the correlation of various fat absorption tests.

*Quantitative criteria* The amount of fat in the faeces can be determined by the analysis of a single sample or of a cumulative specimen collected over a known period. If the first method is used, the result can be expressed only as a percentage of the faecal dry weight, and the result interpreted in relation to more or less arbitrary normal limits. It is known that great variation in faecal dried weight occurs with different or similar diets, depending upon the amount of the unabsorbed residue (Pratt, 1934, Wang, Hogden, and Genther, 1939, Macy, 1942). Even if careful dietary control is exercised, great variation in the non-fatty residue may change the fat percentage from abnormal to normal levels, or *vice versa*, and this may particularly happen when the fat absorption is only slightly depressed. Furthermore, phasic variations in absorption are not uncommon, making the examination of only one small sample of faeces undesirable. In addition to these difficulties the normal physiological range has not been satisfactorily agreed, and figures for the upper limit of normal faecal fat are given by various authors as ranging from 15 to 50 per cent (Hutchison, 1919, Fowweather, 1926, Sheldon and Harrison, 1927, Harris and Harris, 1942). It can be seen by reference to Table I, and to our findings in individual cases

in Tables III to V that a high dried faecal fat percentage was found in some of the control series. Furthermore, in a number of abnormal subjects the diagnosis could not have been made had attention been paid only to this percentage. This method of investigation thus cannot be relied upon for the differentiation of the normal from the abnormal unless the observed defect is gross, and in such cases there are invariably other associated symptoms.

TABLE II

	Days duration of observation	Number of obser- vations	Daily fat intake (gm )	Daily fat excretion (gm )	Percentage absorption
Deucher (1898)	3	1	203	6.3	96.9
Gross (1912)	2	1	168	4.2	97.5
Garrod and Hurtley (1912)	3	1	177	1.4	99.2
Schmidt (1915)	3	3	111	6.1	94.5
Spriggs and Leigh (1915)	3	1	136	5.4	96.0
Pratt (1934)	3	7	132	3.3 to 13.2	90 to 97.5
Wang, Hogden, and Genther (1939)	6	6	72 to 88	1.8 to 3.4	97
Macy (1942)	5	515	60 to 110 (79.3 $\pm$ 16.58)	3.47 ( $\pm$ 0.44)	96 to 97
Rekers, Abels, and Rhoads (1943)	3	2	120 to 130	—	96 to 97
Rekers, Abels, and Rhoads (1943)	3	2	200 to 210	—	92 to 94
Present series	2 to 4	50	50	2.5 $\pm$ 2	95 $\pm$ 4

and signs upon which a diagnosis could also be made. For similar reasons the method is of no value in determining the cure of steatorrhoea as has been assumed in many investigations.

In the second method the faeces are collected over a period of two to five days. If the output is correlated with the dietary intake, the percentage absorption can be calculated. The amount of fat absorbed is clearly equal to the difference between the quantity ingested and the faecal fat, plus any of the latter which is derived from a non-dietary source. Muller (1893) demonstrated that 28 per cent of the dried weight of the faeces in a fasting human subject consisted of fat. Holmes and Kerr (1923) showed that faecal fat differed from the fat in the food in various ways, and interpreted this as evidence for fat excretion. It is probable, however, that different fatty acids may be selectively absorbed (Langworthy, 1923, Holt, Tidwell, Kirk, Cross, and Neale, 1935) which would result in changes of iodine value, melting-point, and other characteristics. Sperry (1926*a*) made extensive investigations of this problem and concluded that a significant proportion of the normal faecal fat was derived from non-dietary sources, which could not be entirely accounted for by biliary secretion, bacterial synthesis, or the desquamation of epithelial cells (Sperry, 1926*b*, Sperry and Angevine, 1932, Sperry, 1932). In addition to this excreted lipid material, of which about half is unsaponifiable, varying amounts of volatile lower fatty acids may be derived from carbohydrate or protein. The estimation of the non-dietary fraction

and consistency, and in an appreciable number of cases of idiopathic steatorrhoea, the presence of abnormal fat content could be detected only by quantitative fat analyses. Stools were usually passed once or twice a day. Many of the proved cases of steatorrhoea had long periods of normal bowel habits, and, not infrequently, of constipation. Thus, Case 51, who had been under observation since childhood for coeliac disease, had no intestinal symptoms. She had, however, a refractory macrocytic anaemia, and recurrent severe mouth ulceration. Her faeces were dark and constipated. Fat balance tests showed only 82 per cent absorption.

Microscopical examination of the faeces of idiopathic steatorrhoea and tropical sprue usually show an excess of fatty acid crystals. Occasionally in severe diarrhoea muscle fibres may be seen, but usually no other abnormal constituents. Hurst (1942) considered that the microscopical features were so characteristic that quantitative estimation of the fat was unnecessary. While the presence of excess fatty acid frequently indicates steatorrhoea, we encountered a sufficient number of exceptions, both with and without fatty acid crystals, to make this qualitative method of diagnosis unreliable for our purpose.

### *Discussion*

The essential feature of our series of cases was the presence of an abnormal amount of fat in the faeces, and diarrhoea was not a constant symptom. Four main points may be considered, the quantitative criteria upon which the assessment of normality or otherwise is based, the significance of the percentage hydrolysis and composition of faecal fat, the relationship of intestinal hurry to malabsorption of fat, and the correlation of various fat absorption tests.

*Quantitative criteria* The amount of fat in the faeces can be determined by the analysis of a single sample or of a cumulative specimen collected over a known period. If the first method is used, the result can be expressed only as a percentage of the faecal dry weight, and the result interpreted in relation to more or less arbitrary normal limits. It is known that great variation in faecal dried weight occurs with different or similar diets, depending upon the amount of the unabsorbed residue (Pratt, 1934, Wang, Hogden, and Genther, 1939, Macy, 1942). Even if careful dietary control is exercised, great variation in the non-fatty residue may change the fat percentage from abnormal to normal levels, or *vice versa*, and this may particularly happen when the fat absorption is only slightly depressed. Furthermore, phasic variations in absorption are not uncommon, making the examination of only one small sample of faeces undesirable. In addition to these difficulties the normal physiological range has not been satisfactorily agreed, and figures for the upper limit of normal faecal fat are given by various authors as ranging from 15 to 50 per cent (Hutchison, 1919, Fowweather, 1926, Sheldon and Harrison, 1927, Harris and Harris, 1942). It can be seen by reference to Table I, and to our findings in individual cases

support the view that the excess of faecal fat is derived from unabsorbed material. There does not seem to be any great need for the application of a standard correction to the faecal fat figures in our series. The effect of such a correction would be to emphasize the difference between the normal and abnormal groups. In the Tables the fraction of the faecal fat derived

TABLE IV  
*Tropical Sprue*

Case number	Sex and age	Duration of test (hr.)	Percentage of dried faeces				Percentage hydrolysis of fat	Daily intake (gm.)	Daily excretion (gm.)	Percentage absorption
			Neutral fat	Free fatty acid	Soap	Total fat				
A										
71	M 69	48	9.2	18.6	18.6	46.4	81	50	72.4	—
72	M 53	48	6.0	9.0	11.1	26.1	77	50	17.2	68
73	M 33	48	5.9	11.0	9.6	26.5	78	50	11.4	77
		48	8.0	13.1	11.1	32.2	75	50	7.6	85
74	M 33	48	8.2	14.6	18.8	41.6	80	50	18.1	64
75	F 36	48	3.8	3.9	11.4	19.1	80	50	7.8	84
B										
76	M 34	48	5.2	4.7	8.8	18.7	73	50	10.3	80
77	M 27	48	3.7	5.7	10.6	20.0	82	50	13.3	73
78	M 32	72	6.2	20.9	15.1	42.2	85	50	17.0	66
		72	9.4	19.8	12.4	41.6	77	50	15.6	68
		72	6.4	12.3	14.1	32.8	80	50	20.8	58
79	M 22	72	0.8	3.2	13.5	17.5	96	50	5.3	89
		72	4.5	3.7	7.3	15.5	71	50	4.5	91
80	M 23	72	4.5	4.5	5.4	14.4	69	50	3.1	94
		72	3.9	3.8	10.0	17.7	78	50	6.1	88
81	M 25	48	3.6	2.6	11.3	17.5	80	50	6.2	88
		72	1.7	1.2	13.7	16.6	90	50	6.1	88
82	M 29	72	1.7	3.3	7.9	12.9	87	50	6.6	87
83	M 21	72	5.6	3.9	12.3	21.8	74	50	5.9	88
C										
84	M 23	48	1.7	4.5	6.2	12.4	87	50	4.4	91
85	M 21	48	1.9	4.4	5.7	12.0	84	50	4.9	90
86	M 21	72	2.5	2.9	3.2	8.6	71	50	0.6	99
87	M 30	72	2.2	3.2	5.6	11.0	80	50	4.4	91
88	M 28	48	2.7	1.4	8.5	12.6	78	50	1.9	96
89	M 45	72	3.8	5.1	6.9	15.8	76	50	3.9	92
90	M 22	72	3.1	4.9	5.5	13.5	77	80	1.7	97
91	M 27	72	3.2	2.7	3.9	9.8	68	50	3.4	93
A Relapse			B Recent severe				C Recent 'cured'			

from non-dietary sources has thus been disregarded and the percentage absorption figures are calculated directly from the difference between the amount of fat ingested and that found in the faeces over the comparable period. If the percentage absorption was calculated in this way, it was found to be  $95 \pm 4$  per cent in our controls, the majority exceeding 95 per cent. This figure is in agreement with that of other observers in this field (Table II). In the normal subject the percentage absorption remains within these limits if the fat intake is increased up to 150 gm daily or more. The

of faecal fat as a routine procedure in patients is difficult and there is little evidence to indicate that this fraction was disproportionately increased in

TABLE III  
*Idiopathic Steatorrhoea*

Case number	Sex and age	Duration of test (hr.)	Percentage of dried faeces				Percentage hydrolysis of fat	Daily intake (gm.)	Daily excretion (gm.)	Percentage absorption
			Neutral fat	Free fatty acid	Soap	Total fat				
42	M 25	48	4.1	29.1	13.0	46.2	92	50	18.3	63
43	F 46	48	5.7	12.5	26.8	47.0	88	50	19.4	61
		72	7.2	14.5	23.0	44.7	84	50	9.9	80
		72	9.2	15.2	12.2	36.6	75	50	11.5	77
		72	4.2	8.9	7.1	20.2	79	50	9.7	81
		48	2.0	16.1	14.4	33.4	91	50	8.2	84
44	M 18	48	5.0	18.4	1.0	24.4	80	50	7.1	86
		48	10.1	14.6	8.4	33.1	70	50	14.4	71
		48	8.4	8.8	2.0	19.2	56	50	9.2	82
		72	4.7	12.5	15.0	32.2	85	50	11.5	77
45	M 35	48	23.3	40.4	9.6	73.3	68	50	13.3	73
		48	8.9	31.4	11.1	51.4	83	50	17.6	65
46	M 54	48	4.3	21.5	21.8	47.6	90	50	34.7	31
		48	4.5	14.7	9.2	28.4	84	50	8.8	82
		48	12.3	19.5	8.1	39.9	70	50	11.5	77
47	M 52	48	4.9	6.1	16.5	27.5	82	50	17.6	85
48	M 56	72	5.9	16.5	20.1	48.5	88	50	21.7	57
49	M 50	48	8.5	15.5	13.3	37.3	77	50	14.0	72
50	M 44	48	12.9	4.2	5.9	23.0	44	50	8.5	83
51	F 21	48	6.6	5.8	20.5	32.9	81	50	11.8	76
		48	7.0	8.5	14.7	30.2	77	50	9.6	81
52	M 48	48	4.9	15.7	11.0	31.6	84	50	12.5	75
53	M 50	48	4.3	11.0	3.2	18.5	77	50	4.7	91
		96	5.2	21.0	13.6	39.8	87	50	10.2	80
54	F 48	48	5.3	15.3	6.1	26.7	80	50	5.2	90
55	F 72	48	5.1	27.1	12.3	44.5	88	50	14.0	72
56	F 48	48	4.2	11.1	11.1	26.4	84	50	5.5	89
		96	5.7	13.1	8.7	27.5	79	50	7.7	85
		72	3.9	14.2	8.7	26.8	86	50	10.4	79
57	F 33	48	2.6	16.2	17.8	36.6	95	50	5.5	89
		96	5.2	11.7	6.5	23.4	76	50	10.7	78
58	M 33	96	3.1	5.6	7.6	16.3	80	50	7.6	85
59	F 57	72	3.5	13.2	9.6	26.3	87	50	16.2	68
60	F 36	72	10.3	18.6	15.1	44.0	77	50	10.7	79
61	M 53	72	12.6	14.6	14.0	41.2	70	50	8.4	83
62	M 19	48	4.6	6.3	8.6	19.5	77	50	8.8	83
63	F 64	72	9.5	15.0	16.7	41.2	77	50	6.5	87
		72	8.2	17.2	20.8	46.2	82	50	11.2	78
64	F 23	72	1.8	7.2	10.5	19.5	90	50	9.6	81
65	M 28	72	7.4	21.4	2.4	31.2	76	50	15.7	69
*66	M 50	120	12.2	33.6	4.9	50.7	76	50	33.2	34
67	F 65	72	3.4	8.8	31.2	43.4	92	50	14.3	71
*68	M 31	72	7.4	22.3	2.4	32.1	77	50	6.8	86
69	F 50	72	0.6	4.5	13.0	18.1	97	50	7.5	85
70	F 48	72	6.5	20.7	33.0	60.2	89	50	12.0	76

\* Both these cases, though passing only one large pale stool daily, died within two weeks of these findings

any of the cases under investigation. The ready response of these patients to a low fat diet and the presence of associated signs of defective absorption

in the faeces (Fleckseder, 1908) After complete pancreatectomy in man, lipolysis still occurs (Whipple, Parsons, and Mullins, 1935, Priestley, Comfort, and Radcliffe, 1944) In the cases of pancreatitis in our series normal splitting of faecal fat was demonstrated, and in one the alveolar portion of the pancreas was found at autopsy to be completely atrophic and the pancreatic ducts were filled with calculi Similar observations have been made by Schmidt (1910), Anderson (1938), and Deem and McGeorge (1941) The alleged significance of the percentage hydrolysis in the diagnosis of pancreatic disease is based on the assumptions that there is no alternative source of lipase, and that fat can be absorbed from the intestinal lumen only as fatty acid The former view takes no account of the lipase which has been demonstrated in the gastric juice (Hull and Keeton, 1917, Willstätter and Memmen, 1924), intestinal juice (Boldyreff, 1904, Kalaboukoff and Terronne, 1937), and bacteria (Michaels and Nakahara, 1923) The latter assumption does not accord with the evidence upon which the partition hypothesis of fat absorption is based (Frazer, 1943 *a, b*, Frazer, Schulman, and Stewart, 1944) It may be concluded, therefore, that the percentage hydrolysis of fat in the faeces has little significance, and in particular that it cannot be regarded as a reliable index of normal pancreatic function

The interpretation of changes in the chemical characteristics of faecal fat is at present unsatisfactory Evidence has been put forward that the faeces contain a higher proportion of saturated fat in coeliac disease (Parsons, 1932) This might indicate increased excretion of saturated fats, or a selective difficulty in their absorption, or it might be associated with a deficiency of dehydrogenases We have not been able to demonstrate any constant features in the faecal fat in our series Usually about half of the split fat in the faeces is present as soap, although considerable variations are found from case to case, and from time to time in the same case It is difficult at present to correlate variations in the amount of soap in the faeces with such symptoms as diarrhoea, or those associated with a low level of serum-calcium or serum-sodium It is possible that these difficulties may be partly due to the inadequacy of the data with regard to soap in the faeces, as only the gross value of the petroleum-ether insoluble fraction is usually determined While low sodium and calcium values may be partly attributed to interference with ionic absorption, due to the presence of an excess of fatty acid in the intestinal lumen, it is doubtful whether this constitutes a major factor in the production of these associated disturbances It is concluded that, on the data available, the chemical composition of faecal fat and the percentage of soap cannot be given any useful clinical interpretation

*The relationship of intestinal hurry to malabsorption of fat* It has been suggested (Rosenthal, 1940, O'Sullivan and Moore, 1941) that the rapid rate of passage of intestinal contents through the alimentary tract might be an important factor in the production of a fault in fat absorption It is clear that the measurement of the retention time in the alimentary tract in man by the use of charcoal or other markers is only a crude method which does



majority of our observations were made on patients stabilized on a diet containing 50 gm of fat per diem, and, in these circumstances, a percentage fat absorption of less than 90 could not be regarded as normal. In practice it was found that cases with a percentage absorption of less than 85 invariably showed associated signs and symptoms confirming the presence of a fat absorption defect. If the figure was between 85 and 90 and the pre-

TABLE V  
*Pancreatitis*

Case number	Sex and age	Duration of test (hr)	Percentage of dried faeces				Percentage hydrolysis of fat	Daily intake (gm)	Daily excretion (gm)	Percentage absorption	Remarks
			Neutral fat	Free fatty acid	Soap	Total fat					
92	F 58	48	2.4	27.8	21.0	51.2	95	50	40.9	18	Autopsy
93	F 65	48	6.0	20.0	9.6	35.6	83	20	12.5	38	Operation
94	F 59	48	1.8	5.8	4.9	12.5	86	50	6.6	87	Autopsy
95	M 55	72	11.2	7.3	8.9	27.4	56	50	8.7	83	Operation
96	F 32	72	7.2	8.3	3.3	18.8	62	50	5.3	89	Diabetes, recurrent pale stools
97	F 18	48	7.0	7.9	6.9	21.8	68	50	7.0	86	Coeliac disease, severe bronchiectasis
98	M 50	48	3.7	10.3	4.7	18.7	80	50	4.6	91	Autopsy

sence of the defect was not clearly supported by other clinical manifestations, reinvestigation was made.

A third method which may with advantage be employed in the detection of fat absorption faults is the use of a chemically recognizable or labelled fat. This has not been done in the present series, but development of such a method is under investigation. Provided that the characteristics or labelling of the fat are not altered in the intestinal lumen, this method should have many advantages over those at present available. It is concluded that the only reliable method at the present time for the detection of fat absorption faults, especially in those cases in which there is no gross defect, is the fat balance technique.

*The significance of percentage hydrolysis and composition of faecal fat.* Seventy to 80 per cent of the faecal fat is normally present as fatty acid or soap. The degree of splitting of the neutral fat has been interpreted by some workers as being an index of pancreatic function. It is claimed that a low hydrolysis points to a deficiency of pancreatic juice, and that 70 per cent or more hydrolysis excludes the possibility of pancreatic disease (Müller, 1887, Harper, 1930, Parsons, 1932). However, as Garrod and Hurtle (1912) pointed out, observations can be found in which normal splitting and pancreatic diseases are present, and abnormal splitting and no pancreatic disease. It can be shown in animals that complete removal of the pancreas has no significant effect upon percentage hydrolysis of fat.

observation The increase can be partly accounted for by increasing awareness of the varied clinical manifestations, so that investigations of refractory macrocytic anaemia, atypical pernicious and hypochromic anaemias, colitis, chronic enteritis, and infantilism could not be considered complete unless a fat balance test were carried out A more important factor may be an actual increased incidence of these anomalies Snell (1939), for example, encountered only 32 cases in 10 years in a large amount of material at the Mayo Clinic An increased incidence of coeliac disease was recorded during the war of 1914-18 (Miller, 1921) and in the war of 1939-45 a similar increase has been noted (Parsons, 1945) With few exceptions the patients with idiopathic steatorrhoea feed well when allowed an unrestricted selection, but war-time shortages have severely limited protein intake and resulted in the ingestion of types of fats which normally would have been avoided Thus patients with a fat absorption defect may remain adjusted by dietary selection in peace-time, which becomes impossible in times of war If this is so, minor and potentially important anomalies of fat absorption are more common than has hitherto been supposed

### *Summary*

1 Fat balance tests on a 50 gm fat intake have been carried out on 120 patients In 41 control patients more than 95 per cent was usually absorbed, with variations between 91 and 99 per cent In 29 cases of idiopathic steatorrhoea the average absorption was 73 per cent (range 29 to 91) Results in other types of steatorrhoea are also presented

2 Microscopical examination of faeces, although frequently revealing excess fatty acid crystals, was not found to be a certain method of detecting abnormal fat absorption

3 While faeces containing abnormal amounts of fat are often pale and more bulky than usual, they may be perfectly normal in colour and consistency

4 The percentage fat in dried faeces has not been found to be a reliable criterion in the differentiation of normal from abnormal absorption

5 Percentage hydrolysis of faecal fat was found to be of little value in the diagnosis of pancreatic disease

6 Malabsorption of fat could not be attributed to small intestinal hurry

7 It is suggested that the correlation of dietary and faecal fat as fatty acid is sufficient for the detection of a fat absorption defect There appears to be little advantage at present in the further differential analysis of faecal fat

8 The absorption of 70 to 80 per cent of ingested fat in the absence of post-absorptive systemic lipaemia is discussed

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not differentiate between the rate of travel of the intestinal contents through the various parts of the bowel. So far as the absorption of fat is concerned, it is only alteration in the period of retention in the small intestine which could be significant, and this can be determined only by radiography. Care must be exercised in comparing the behaviour of a barium meal with that of normal food, especially if absorption is deranged. In those cases of diarrhoea in our series in which charcoal passed through the alimentary tract within seven hours of ingestion, fat absorption was normal, exceeding 95 per cent in all cases. In the 35 cases in the series with a proved fat absorption defect which were investigated radiographically, there was no evidence of increased rate of passage through the small intestine. All these cases showed varying degrees of the 'deficiency pattern' (Camp and Snell, 1934, Mackie and Pound, 1935, Kantor, 1940, Golden, 1941), which one would expect to be associated with delay rather than hurry. The total retention time in the alimentary tract was, however, frequently decreased. It must be concluded that, when intestinal hurry can be demonstrated in these cases, the colon is primarily involved and consequently the defective absorption of fat cannot be attributed to lack of time.

*Correlation of fat absorption tests.* In addition to the investigation of the amount of fat in the faeces, the absorption of fat may also be investigated by examination of the blood during the post-absorptive period either by chemical analysis or the chylomicrograph (Fish and Gage, 1924, Frazer and Stewart, 1939). In the normal subject a characteristic lipaemia can be demonstrated in the systemic blood during four hours after ingestion of fat. It was a striking feature of many of our cases of defective fat absorption that while fat balance tests indicated that 70 to 80 per cent absorption had occurred, there was little or no change in the blood-fat. The constantly flat chylomicrograph curve, and correspondingly low value for blood-fat obtained on chemical analysis, are difficult to explain in these cases unless it is assumed that the fat is leaving the intestine by some pathway other than the thoracic duct and systemic blood. If normal subjects ingest a standard fat meal with added lipase, a somewhat similar phenomenon of absorption without the normal post-absorptive systemic sequelae can be demonstrated (Frazer, 1943 a, b). On the basis of animal experiments this phenomenon has been explained as being due to the absorption of fatty acid direct to the liver *via* the portal vein. It is not impossible that some such mechanism of absorption may account for the observations made in cases of steatorrhoea. In these circumstances absorption does not appear to be so complete as that found when normal fat/fatty acid partition occurs.

Many more cases of anomalous fat absorption have been encountered than was anticipated at the outset of these investigations. For example, 38 cases of idiopathic steatorrhoea in addition to a number of other closely allied conditions have been observed over the past four years in a general hospital which has had much of its accommodation devoted to military requirements. Review of our diagnostic criteria and case material has not altered this

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# CHANGES IN THE PARKINSONIAN SYNDROME IN THE TWENTIETH CENTURY<sup>1</sup>

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## *Introduction*

It is the purpose of the present paper to examine the clinical features of 320 cases of the Parkinsonian syndrome collected from records throughout the present century in an attempt to assess changes in aetiology and modifications in clinical form

By the beginning of the twentieth century the clinical features of paralysis agitans had been fully described in the works of Parkinson (1817), Buzzard (1882), Charcot (1892), and Gowers (1888). Clinical accounts appearing in the early years of the century were those of Manschot (1904) and Mendel (1911). The contribution of Hunt (1917) subdivided paralysis agitans into pre-senile, senile, juvenile, and symptomatic forms. He considered that the juvenile form was an abiotrophy, and proposed the name 'progressive atrophy of the globus pallidus'. He suggested that some adult cases might belong to this pathological group.

An important new aetiological factor in the production of a Parkinsonian state became active in this country in the spring of 1918. Harris (1918) and Hall (1918) published descriptions of an epidemic disease presenting as an acute ophthalmoplegia with bulbar symptoms. Subsequently the condition was identified with von Economo's encephalitis lethargica. Hall (1918) remarked on the facial expression of an encephalitic patient as 'so suggestive of Parkinson's mask that I thought she must have paralysis agitans'. Batten and Still (1918) described the mask-like appearance of the face in 'epidemic stupor' prevalent among children at the time. Buzzard (1918) and Wilson (1918) also commented on the resemblance between encephalitic patients and cases of paralysis agitans. The encephalitic origin of an extrapyramidal syndrome similar to paralysis agitans became established.

Critchley (1929) drew attention to arteriosclerotic Parkinsonism, a form described in earlier case records as paralysis agitans and cerebrovascular degeneration. The clinical association of tabes and paralysis agitans was attributed by Wilson and Cobb (1924) to syphilitic mesencephalitis. A rare syndrome of Parkinsonism with additional features of spasticity and mental deterioration was described by Jakob (1921) and Creutzfeldt (1920). The initial stages of progressive lenticular degeneration may present as a Parkinsonian state, later complicated by the development of mental changes,

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*Chronological arrangement* In the earlier years of the twentieth century paralysis agitans was the predominant form of Parkinsonism. During the years 1920 to 1930 large numbers of cases of encephalitic Parkinsonism appeared as an immediate result of the epidemic of encephalitis lethargica. After 1930 the epidemic subsided, but cases of encephalitic Parkinsonism still occurred as the delayed result of an earlier encephalitic infection. The distinction of the various forms of Parkinsonism was further complicated by the development of a clinical picture resembling encephalitic Parkinsonism in patients who had no history of acute or subacute encephalitis. The cases have been divided into these three chronological periods to examine any changes occurring in the main forms of Parkinsonism.

1900 to 1919 One hundred cases recorded before the production of Parkinsonism by encephalitis lethargica

1920 to 1930 One hundred cases recorded during the epidemic

1931 to 1942 One hundred and twenty cases recorded during the period after the epidemic

*Clinical analysis* The following clinical aspects of the Parkinsonism syndrome have been considered—age distribution, duration of symptoms, significant past illness, mode of onset, symptoms and signs, clinical variants. As most of the cases were observed on a single occasion, the relative prognosis could not be assessed, but the duration of symptoms prior to attendance at hospital gave some indication of the course of the different forms.

*1900 to 1919* The records of 100 cases were examined to obtain a picture of the Parkinsonian syndrome prior to the epidemic period. Marshall Hall's term paralysis agitans was in general use at this time, and was the diagnosis made in every case, with one exception described as Parkinson's disease. The age distribution arranged in decades showed a modal age of onset between 51 and 60 years. The majority of cases (88) occurred over the age of 40 years. The duration of symptoms prior to observation varied from two months to 16 years. In about half the cases (53) it did not exceed two years. A disease described as influenza preceded the onset of symptoms in two cases, but neither of these was atypical in its form. The mode of onset in the majority of cases (78) consisted of shaking of a limb. Thirteen patients complained of weakness. Stiffness or pains in the limbs were less common presenting symptoms. Mental symptoms were unusual, and occurred in seven older patients. The type of disorder was involuntional or senile. On examination the dominant sign was tremor, which was present in 98 cases, usually first involving the fingers or wrist of the right upper limb. Rigidity was recorded as present in 62 cases. Weakness frequently affected the tremulous upper limb, but also might be associated with rigidity of the lower limbs. The right side of the body was predominantly affected in 47 cases, the left in 32, and both equally in 21. Salivation was excessive in three cases. Ocular abnormalities were present in 10 cases, but in four of these the defect was simple anisocoria. Two cases showed defective convergence.



spasmodic movements, and contractures. Degeneration of the globus pallidus with development of Parkinsonian symptoms has resulted from exposure to toxic quantities of nitrous oxide, carbon monoxide, carbon disulphide, manganese, potassium cyanide, and barbiturates (Alexander, 1942). Electrocution has been followed by the development of Parkinsonism. A local lesion in the basal ganglia whether traumatic, vascular, or neoplastic, may produce unilateral Parkinsonian signs. Any direct causal relationship between general trauma, mental or physical, and the appearance of Parkinsonian symptoms has not been proved.

### *Material*

The clinical material on which the present paper is based consists of 33 cases collected from early in-patient records at University College Hospital, 235 cases from out-patient and in-patient records at Maida Vale Hospital for Nervous Diseases, and 52 cases from the private records of Dr Russell Brain. The use of routine hospital records for a clinical analysis may be criticized, because the detail in which physical signs are recorded tends to vary. On the other hand data from a large number of observers favours statistical accuracy. Only the major symptoms and signs of Parkinsonism which seemed adequately observed throughout the series of cases were selected for consideration.

*Classification* As in recent years the diagnosis of Parkinsonism was made in some cases without reference to the aetiology, the following diagnostic criteria have been used to distinguish the main forms of Parkinsonism.

Paralysis agitans usually occurs in the second half of life and tends to affect otherwise healthy subjects. The onset is characterized by rhythmical tremor of a limb and some degree of rigidity. Pupillary abnormalities and disorders of ocular movement form no part of the picture, apart from slowness of movement and fixation of gaze when rigidity is marked. Autonomic instability and other signs of hypothalamic disturbance, including drowsiness, may sometimes occur in progressive phases of the disease.

Encephalitic Parkinsonism develops during or after an attack of encephalitis lethargica. The Parkinsonism is complicated by the presence of some additional symptoms and signs, including abnormalities of ocular movement and pupillary function, disturbances of sleep rhythm, and mental changes.

Indeterminate Parkinsonism is the term used in the present paper for cases resembling encephalitic Parkinsonism in clinical features, but differing in the absence of a history of an attack of encephalitis lethargica.

Arteriosclerotic Parkinsonism could not be satisfactorily distinguished from paralysis agitans in the available case material. In earlier records these cases were described as 'paralysis agitans and cerebrovascular degeneration'. This form of Parkinsonism has, therefore, been included with paralysis agitans.

Other rare forms include syphilitic vascular Parkinsonism and the Jakob-Creutzfeldt syndrome.

Some clinical variants of the classical form were included. Three cases developing symptoms before the age of 31 years might be described as examples of juvenile paralysis agitans. None gave a history of a preceding infection, tremor in all was more prominent than rigidity, the pupils and ocular movements were normal. Two women with onset after the age of 70 years belonged to the senile variety, and both showed well marked tremor. The diagnoses of cerebral degeneration, vascular disease, and doubtful paralysis agitans were made in two cases which conformed in clinical features with Critchley's arteriosclerotic Parkinsonism. Complicating diseases were rare, diabetes was present in one case. For their age the patients were exceptionally healthy, and hypertension was uncommon.

*1920 to 1930* During the years 1920 to 1930 a series of 100 cases of the Parkinsonian syndrome showed a less uniform clinical picture than in the preceding period, due to the production of cases of Parkinsonism by encephalitis lethargica. Thirty-four cases resembled paralysis agitans in their clinical features. Fifty-four cases followed an attack of encephalitis lethargica. Eleven cases conformed with encephalitic Parkinsonism in type, but the development of symptoms was not preceded by symptoms of encephalitis. These have been called indeterminate Parkinsonism. There was one example of tabes and paralysis agitans, which will be described with a case of syphilis and Parkinsonism in the next series.

*Paralysis agitans (Idiopathic Parkinsonism)* The age distribution again showed a modal age of onset between 51 and 60 years of age. As in the previous series the duration of symptoms prior to attendance for treatment in just over half the cases (56 per cent) did not exceed two years. The signs and symptoms were unchanged apart from a slight increase of cases showing rigidity (68 per cent), and in defects of convergence. No examples of the juvenile or senile forms occurred. The only complicating diseases were hysteria in one case and arteriosclerosis in another.

*Encephalitic Parkinsonism* The causative attacks of encephalitis lethargica occurred during the years 1918 to 1929, with peak years falling in 1920 and 1924, thus corresponding with the incidence in this country (Registrar General's statistical review, 1918-29) and throughout the world (Matheson Commission Survey, 1929). The interval between the symptoms of the acute attack and the development of the Parkinsonian sequelae seldom exceeded six months, and frequently the acute illness blended with the chronic disability. The age distribution showed a marked contrast with that of paralysis agitans. Encephalitic Parkinsonism in this period was a malady of the first half of life, young adults being principally affected. The modal age of onset was in the second decade. The duration of symptoms varied between three weeks and six years, but the majority of cases (72 per cent) presented themselves for treatment of Parkinsonism within two years. Encephalitis lethargica during the epidemic period produced an advanced degree of Parkinsonism which developed rapidly. Shakiness, although less

TABLE I  
*Mode of Onset*

[illegible]

TABLE II  
*Symptoms and Signs*

Series	Symptoms and Signs										
	1900 to 1919		1920 to 1930				1931 to 1942				
	Paralysis agitans	100 %	Paralysis agitans	%	Encephalitic Parkinsonism	%	Indeterminato Parkinsonism	%	Paralysis agitans	Encephalitic Parkinsonism	Indeterminato Parkinsonism
Number of cases	7	7	—	34	54	13	24	4	52	21	42
Mental symptoms	—	—	—	12	—	—	—	—	7	7	20
Sleep disorder	78	78	—	—	13	24	4	—	7	20	4
Parkinsonism appearance	98	98	27	80	5	9	4	—	—	4	9
Tremor	98	98	30	89	47	87	10	—	21	90	37
Rigidity	62	62	38	70	38	70	8	—	21	90	31
Salivation	3	3	23	68	47	87	9	—	37	71	80
	—	—	3	9	22	41	4	—	3	58	0
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of paralysis agitans After the epidemic of encephalitis these exceptional forms became common Most of them showed ocular abnormalities and have been included in the group of indeterminate Parkinsonism One hundred and twenty cases of Parkinsonism observed during these years consisted of 52 cases of paralysis agitans, 24 cases of declared encephalitic Parkinsonism, 42 cases of indeterminate Parkinsonism, one case of the Jakob-Creutzfeldt syndrome, and one case of Parkinsonism and syphilis

*Paralysis agitans* As in the earlier series, paralysis agitans showed a modal age of onset in the sixth decade The duration of symptoms in just over half the cases did not exceed two years An infection described as congestion of the lungs preceded the onset of shaking in one case The symptoms and signs resembled the previous groups of paralysis agitans, and again there was a right sided predominance No juvenile cases occurred in this group The senile cases numbered eight Two cases might be distinguished as arteriosclerotic Parkinsonism The only complicating disease recorded was auricular fibrillation in a man aged 63 years

*Encephalitic Parkinsonism* The interval between the causative attack of encephalitis and the appearance of Parkinsonian sequelae varied between the extremes of an immediate onset to a latent period of 19 years Most of the cases, in contrast with those of the epidemic period, were characterized by a latent interval of some years During the epidemic period most of the cases developed Parkinsonian sequelae in the year after the attack of encephalitis The age of incidence of acute encephalitis and encephalitic Parkinsonism differed only by weeks or months After the epidemic subsided, cases with a period of latency affected the age of incidence The modal age of onset occurred in the third decade, and the large number of cases occurring between the ages of 11 and 20 years had practically disappeared The duration of symptoms prior to attendance at hospital varied from three months to 18 years and in over half the cases (66 per cent.) exceeded two years The onset was insidious and the course prolonged Shakiness was more prominent as an initial symptom than in the previous series of encephalitic Parkinsonism and occurred in 13 cases (54 per cent) Stiffness, weakness combined with shakiness or stiffness, and oculogyric crises were other modes of onset Mental symptoms showed approximately the same incidence as in the preceding series, but disorder of mood characterized by depression was more common than major lack of emotional control Four patients complained of disturbance of sleep rhythm Tremor was evident on examination in 21 cases (90 per cent) and was frequently described as 'fine', 'pill rolling', or 'rhythmical', adjectives formerly restricted to the tremor of paralysis agitans There was no definite predominance in the side of the body affected Rigidity and salivation were less marked than in encephalitic Parkinsonism of the epidemic period Eye signs were common and occurred in 17 cases (71 per cent) A defect of accommodation was the abnormality most frequently present, but usually in association with other pupillary anomalies Six cases had oculogyric crises

predominant than in paralysis agitans, was the presenting symptom in 21 cases (39 per cent). Stiffness, weakness associated with stiffness, and sleep disorders were often initial symptoms. Mental symptoms were considerably more prominent than in paralysis agitans and were present in 13 cases (24 per cent). The type of disorder found was usually one of mood resulting in emotional instability and spontaneous or excessive laughter. Some patients showed emotional apathy with loss of affection for parents and lack of interest in work. Such mental disturbances were common in patients infected in their teens or early twenties. Encephalitis producing mental sequelae in older patients resulted in depression and delusions. Recurrence of sleep disturbance, consisting of nocturnal insomnia and diurnal lethargy, was associated with Parkinsonism in five cases (9 per cent). Rigidity of the limbs on objective examination was more pronounced than in paralysis agitans and occurred in 47 cases (87 per cent). Tremor showed a reduced incidence and was recorded in 38 cases (70 per cent). Its character differed from the tremor occurring in paralysis agitans, and it was described as coarse tremor or shaking rather than possessing a rhythmical quality. The right side of the body was principally affected in 22 cases (41 per cent). A generalized distribution of signs with the right side predominantly affected was the commonest form. Restriction to one limb, in contrast to the findings of Hall (1923), was unusual and occurred in only four cases. Twenty-two cases (41 per cent) showed excessive salivation, a considerable increase contrasted with the incidence of this symptom in paralysis agitans (3 per cent). Eye signs were the chief additional features of encephalitic Parkinsonism and were present in 39 cases (72 per cent). Oculogyric crises occurred in five cases (9 per cent). The commonest manifestation, present in 21 cases (39 per cent), was a defect of accommodation, usually combined with defective convergence and other abnormalities such as ptosis, weakness of elevation, nystagmus, irregular unequal pupils, and impaired light reaction. Isolated defects of convergence and accommodation were rare.

*Indeterminate Parkinsonism* This small group of 11 cases resembled encephalitic Parkinsonism in the incidence of mental symptoms, rigidity, sleep disorders, salivation, and ocular abnormalities. None of the cases had a history of encephalitis lethargica, although three adult patients described an indefinite illness prior to the development of symptoms. The age of onset was variable, but with one exception all cases occurred prior to the sixth decade.

*1931 to 1942* During these years the distinction between the different forms of Parkinsonism became increasingly difficult. The difference in age of incidence between encephalitic Parkinsonism and the degenerative forms was less well defined. Patients affected with encephalitis in their twenties were developing Parkinsonism at an age not uncommon for the onset of paralysis agitans. Prior to 1920 generalized forms of rapid onset and rigid forms, specially of hemiplegic distribution, were recognized as rare variants.

of paralysis agitans After the epidemic of encephalitis these exceptional forms became common Most of them showed ocular abnormalities and have been included in the group of indeterminate Parkinsonism One hundred and twenty cases of Parkinsonism observed during these years consisted of 52 cases of paralysis agitans, 24 cases of declared encephalitic Parkinsonism, 42 cases of indeterminate Parkinsonism, one case of the Jakob-Creutzfeldt syndrome, and one case of Parkinsonism and syphilis

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*Encephalitic Parkinsonism* The interval between the causative attack of encephalitis and the appearance of Parkinsonian sequelae varied between the extremes of an immediate onset to a latent period of 19 years Most of the cases, in contrast with those of the epidemic period, were characterized by a latent interval of some years During the epidemic period most of the cases developed Parkinsonian sequelae in the year after the attack of encephalitis The age of incidence of acute encephalitis and encephalitic Parkinsonism differed only by weeks or months After the epidemic subsided, cases with a period of latency affected the age of incidence The modal age of onset occurred in the third decade, and the large number of cases occurring between the ages of 11 and 20 years had practically disappeared The duration of symptoms prior to attendance at hospital varied from three months to 18 years and in over half the cases (66 per cent) exceeded two years The onset was insidious and the course prolonged Shakiness was more prominent as an initial symptom than in the previous series of encephalitic Parkinsonism and occurred in 13 cases (54 per cent) Stiffness, weakness combined with shakiness or stiffness, and oculogyric crises were other modes of onset Mental symptoms showed approximately the same incidence as in the preceding series, but disorder of mood characterized by depression was more common than major lack of emotional control Four patients complained of disturbance of sleep rhythm Tremor was evident on examination in 21 cases (90 per cent) and was frequently described as 'fine', 'pill rolling', or 'rhythmical', adjectives formerly restricted to the tremor of paralysis agitans There was no definite predominance in the side of the body affected Rigidity and salivation were less marked than in encephalitic Parkinsonism of the epidemic period Eye signs were common and occurred in 17 cases (71 per cent) A defect of accommodation was the abnormality most frequently present, but usually in association with other pupillary anomalies Six cases had oculogyric crises

### TABLE III

## Eye Signs

Series	1900 to 1919			1920 to 1930			1931 to 1942		
	Form of Parkinsonism	Paralysis agitans 100 %	Paralysis agitans 34 %	Encephalitic Parkinsonism 64 %	Indeterminate Parkinsonism 11 %	Paralysis agitans 52 %	Encephalitic Parkinsonism 24 %	Indeterminate Parkinsonism 42 %	
Number of cases		10	8	30	10	4	17	26	
Number of cases with ocular defects		10	21	72	90	76	71	62	
Oculogyric crises		—	—	5	—	—	6	4	
Ptosis		1	—	9	—	—	25	9	
Defect of convergence		2	5	37	18	—	1	2	
Defect of elevation		1	15	20	4	38	42	48	
Defect of elevation		1	—	—	36	—	17	19	
Nystagmus		1	—	—	9	—	—	8	
Strabismus		1	—	8	2	—	—	—	
Unequal pupils		1	—	14	18	—	—	2	
Irregular pupils		1	—	3	—	—	—	48	
Dilated pupils		4	2	37	9	—	42	—	
Contracted pupils		—	6	30	4	19	42	17	
Defective reaction to light		—	—	11	1	19	84	1	
Defective reaction on accom-		—	—	1	—	19	—	24	
modation		—	—	18	—	—	—	—	
Isolated defects of conver-		—	—	22	3	—	—	96	
gence and accommodation		—	—	2	27	—	38	26	
Defects of convergence and		—	—	39	4	—	10	34	
accommodation and other		—	—	7	3	38	126	72	
abnormalities		—	—	37	4	—	8	308	

TABLE IV  
*Side Affected*

## Side Affected

Series	1900 to 1919						1920 to 1930						1931 to 1942								
	Paralysis agitans			Indeterminato Parkinsonism			Paralysis agitans			Encephalitic Parkinsonism			Paralysis agitans			Encephalitic Parkinsonism			Indeterminato Parkinsonism		
	100 %	%	Number of cases	100 %	%	Number of cases	100 %	%	Number of cases	100 %	%	Number of cases	100 %	%	Number of cases	100 %	%	Number of cases	100 %	%	Number of cases
Form of Parkinsonism																					
Number of cases																					
Right	47	47	10	47	22	41	4	38	20	38	0	36	11	33	33	33	33	33	33	33	33
Left	32	32	12	36.5	14	26	1	9	19	37	10	42	21	60	50	50	50	50	50	50	50
Bilateral	21	21	0	17.5	18	33	0	55	13	25	7	17	7	17	7	17	7	17	7	17	17

*Indeterminate Parkinsonism* This form of Parkinsonism became common in the years after the epidemic. Forty-two out of a series of 120 cases of Parkinsonism were of this type. As the interval in years since the epidemic period increased, the fresh cases of indeterminate Parkinsonism appeared in progressively later age groups. In an attempt to show this change the cases have been subdivided into three groups depending on the date of onset of symptoms, prior to 1931, during 1931 to 1936, and during 1937 to 1942.

Age groups in decades	Prior to 1931	1931 to 1936	1937 to 1942
11 to 20	4	2	—
21 „ 30	3	5	3
31 „ 40	2	3	5
41 „ 50	—	3	5
51 „ 60	—	—	4
61 „ 70	—	—	3

Although the number of cases is small it appears that there is a definite rising trend in the modal age of onset. Up to 1931 it falls in the second decade, in 1931 to 1936 in the third decade, and in 1937 to 1942 in the fourth and fifth decades. This variation in the age of onset suggests that these cases of Parkinsonism were the deferred result of an aetiological factor active in the first half of life during 1920 to 1930. None of the patients gave an unequivocal history of encephalitis. Contact through nursing a case of encephalitis lethargica in 1931 directly preceded the onset of symptoms in a woman aged 34 years. Although the commonest presenting symptom was shakiness, occurring in 19 cases (45 per cent), it was less prominent than in declared encephalitic Parkinsonism, stiffness, weakness, and slowness in varying combination, sleep disturbance, oculogyric crises, and mental symptoms were other modes of onset. The symptoms and signs differed slightly from encephalitic Parkinsonism in the predominance of rigidity over tremor. Rigidity occurred in 36 cases (86 per cent) and tremor in 31 (74 per cent). The left side of the body was predominantly affected in 21 cases (50 per cent), the right in 14 (33 per cent), and both equally in seven cases (17 per cent). Abnormal mental states were recorded in four cases, and disturbances of sleep in nine. Excessive salivation was more common than in paralysis agitans. Abnormalities of ocular movement and pupillary function occurred in 26 cases (62 per cent). The commonest abnormality was defective contraction of the pupils on accommodation in 14 cases (34 per cent), but in 13 of these multiple abnormalities were present. Four cases had oculogyric crises. Hypertension and paroxysmal dyspnoea were associated with Parkinsonism in a woman aged 54 years, and another patient, a woman aged 58 years, was deaf and dumb.

*Other forms of Parkinsonism* *The Jakob-Creutzfeldt syndrome* One patient with onset in middle life of weakness and stiffness of the legs, reflex changes of pyramidal type, striatal poverty of movement, slurred speech, and mental changes presented the clinical features of this syndrome.

*Neurosyphilis and Parkinsonism* Wilson and Cobb (1924) described a small number of cases in which paralysis agitans was present in association with



tabes They attributed this clinical combination to the result of a syphilitic meningoencephalitis complicating tabes Some authorities consider that the association is a chance one due to the occurrence of two relatively common conditions in the same patient In the 1920 to 1930 series of cases there was one example of tabes and paralysis agitans, and in the 1931 to 1942 series

TABLE V  
*Age of Onset*  
Paralysis agitans

1900 to 1920		1921 to 1930			1931 to 1942		
Age groups in decades	Number of cases	Age groups in decades	Number of cases	%	Age groups in decades	Number of cases	%
21 to 30	3	21 to 30	0	0	21 to 30	0	0
31 " 40	8	31 " 40	0	17.5	31 " 40	2	3.8
41 " 50	10	41 " 50	5	15	41 " 50	10	19
51 " 60	47	51 " 60	15	44	51 " 60	19	37
61 " 70	24	61 " 70	8	23.5	61 " 70	13	25
71 " 80	2	71 " 80	0	0	71 " 80	7	13
					91 " 90	1	1.9

Encephalitic Parkinsonism

1921 to 1930			1931 to 1942		
Age groups in decades	Number of cases	%	Age groups in decades	Number of cases	%
11 to 20	20	37	11 to 20	3	12.3
21 " 30	18	34	21 " 30	12	50
31 " 40	9	17	31 " 40	5	21
41 " 50	5	9	41 " 50	1	4.2
51 " 60	0	0	51 " 60	3	12.5
61 " 70	2	3	61 " 70	—	—

Indeterminate Parkinsonism

1921 to 1930		1931 to 1942		
Age groups in decades	Number of cases	Age groups in decades	Number of cases	%
0 to 10	1	11 to 20	6	14
11 " 20	3	21 " 30	11	26
21 " 30	1	31 " 40	10	24
31 " 40	2	41 " 50	8	19
41 " 50	3	51 " 60	4	9.6
51 " 60	1	61 " 70	3	7.4

one of encephalitic Parkinsonism complicated by syphilis The first was a man aged 68 years, who had noticed tremor of the left upper limb for two years, later extending to the right He tended to fall backwards if he stopped abruptly For six months prior to coming under observation as a case of paralysis agitans, he had received antisyphilitic treatment as the blood Wassermann reaction was positive On examination his pupils were unequal and reacted poorly to light and on convergence There was moderate bilateral ptosis His face was expressionless, and there was Parkinsonian tremor and rigidity of the upper limbs, more marked on the left than

the right side. There was slight tremor of the left leg. The reflexes were present in the upper limbs, the knee-jerks and ankle-jerks were absent, and the plantar responses flexor. His gait was shuffling and his attitude typical of paralysis agitans. The cerebrospinal fluid contained 42 lymphocytes per c mm, globulin present, albumin 50 mg per 100 c c. Wassermann reaction + + +, Lange curve 555432100. He was considered to be a case of tabes and paralysis agitans, but alternatively could be classified as a case of syphilitic vascular Parkinsonism. The second case was a man aged 31 years, with a history of treated syphilis and an attack of encephalitis while serving in Indo-China. Four years later he developed oculogyric crises and Parkinsonian symptoms. The pupils failed to react on convergence-accommodation, but were active to light. Although the cerebrospinal fluid was normal, the presence of asymmetrical reflexes with bilateral extensor plantar responses suggested the possibility of a dual infection of the nervous system.

### Discussion

The following problems arise in the discussion of the Parkinsonian syndrome

- 1 Whether an idiopathic form (paralysis agitans) exists
- 2 What clinical features distinguish idiopathic and encephalitic forms
- 3 How cases resembling encephalitic Parkinsonism originate in the absence of a known infection with encephalitis (indeterminate Parkinsonism)

1 Although the present paper is concerned with the clinical aspects of the Parkinsonian syndrome, the pathological grounds for recognizing the existence of an idiopathic form require brief consideration. Most authorities (Bielschowsky, 1921, Lhermitte and Cornil, 1921, Foix and Nicolesco, 1925, Keschner and Sloane, 1931, Wilson, 1940) have described the pathological change as a diffuse degenerative process principally localized in the basal ganglia and their efferent systems, unaccompanied by inflammatory reactions, major vascular lesions, or marked gliosis. Certain investigators (Hunt, 1917, Jakob, 1925, Alexander, 1942) have considered that the large ganglion cells were selectively involved, although Jakob found additional changes secondary to capillary fibrosis. Lhermitte and Cornil (1921) and Foix and Nicolesco (1925) observed a patchy pigmentary degeneration of both large and small ganglion cells, an *état criblé* of the white matter secondary to senile vascular changes, and a mild degree of gliosis. They emphasized that the condition was an abnormal and premature localization of senility in the basal ganglia, and might be associated with degenerative changes elsewhere in the brain, including the frontal cortex.

Other recognized forms of Parkinsonism discussed in the present investigation show certain pathological features which enable them to be distinguished from idiopathic Parkinsonism. Most investigators, including Foix (1921), McAlpine (1923), and Alexander (1942), have found that encephalitic Parkinsonism was characterized by the predominance of cell destruction in

the substantia nigra, and the presence of residual inflammatory changes. Although in longstanding cases the perivascular infiltration and diffuse glial proliferation may resolve, some adventitial fibrosis and coarseness and irregularity of glial fibrils usually persist. The diagnostic lesions in syphilitic vascular Parkinsonism are stated to consist of proliferation of the vascular endothelium, and an infiltration of lymphocytes and some plasma cells in the adventitia and perivascular spaces. In the Jakob-Creutzfeldt syndrome atrophy of the corpus striatum is associated with severe atrophy of the cerebral cortex and degeneration of the corticospinal fibres. The pathological conception of idiopathic Parkinsonism (paralysis agitans) as a presenile degenerative disorder is supported by the characteristic age distribution of the disease tabulated by Souques (1921), Patrick and Levy (1922), and Wilson (1940). The present series also showed a consistent modal age of onset in the sixth decade for cases which in other clinical features resembled classical paralysis agitans.

2 Clinical features selected by different authors as important in distinguishing encephalitic Parkinsonism from paralysis agitans include coarse or absent tremor, rigidity, oculogyric crises, other abnormalities of ocular movement, pupillary anomalies, excessive salivation, psychic disorders, and disturbances of sleep rhythm. Hall (1923), Young (1927), and Keschner and Sloane (1931) found that tremor was frequently absent in encephalitic Parkinsonism and if present tended to be coarse, whereas tremor in paralysis agitans was fine and rhythmical in character. Davison (1942) considered tremor one of the outstanding symptoms of 'post-encephalitic paralysis agitans'. He correlated release of tremor with lesions of the substantia nigra and rigidity with atrophy of the globus pallidus. It is possible that this divergence from the previously accepted symptomatology of encephalitic Parkinsonism, which is not commented on by Davison, may be the result of an increase of tremor in the current type of encephalitic Parkinsonism. The present paper tends to confirm this view, tremor was coarse or often absent in the 1920 to 1930 group of encephalitic Parkinsonism. In the 1931 to 1942 group the incidence increased from 70 to 90 per cent, and the tremor was described as 'fine', 'pill rolling', or 'rhythmical', adjectives formerly restricted to paralysis agitans. The ocular manifestations of encephalitic Parkinsonism consist of various abnormalities of ocular movement and pupillary anomalies including fluttering tremor of the closed eyelids and weakness of convergence and accommodation. The sign of blepharoclonus was originally described by Charcot (1892) in paralysis agitans. Exceptionally, weakness of convergence-accommodation may occur as a manifestation of rigidity in striatal disease other than encephalitic Parkinsonism. It has been described in progressive pallidal degeneration (Hunt, 1917), paralysis agitans (Wilson, 1928), and progressive lenticular degeneration (Wilson, 1940). The ocular defects present in cases of encephalitic Parkinsonism recorded by Hall (1923), Keschner and Sloane (1931), Neal (1942), and Davison (1942) were symptomatic of combined striatal and midbrain tegmental lesions. In

the present paper the variations in incidence of blepharoclonus were not considered, as the sign had not been consistently elicited. The commonest defect in encephalitic Parkinsonism was failure of the pupil to react on accommodation, but it was almost invariably associated with additional pupillary abnormalities and defects of ocular movement. The characteristic feature of encephalitic Parkinsonism, therefore, was the multiplicity of ocular defects. Weakness of convergence occurred occasionally in paralysis agitans associated with fixity of gaze. Of the other signs considered important in the differentiation of encephalitic Parkinsonism, rigidity and salivation, although occurring in paralysis agitans, showed a higher incidence in the encephalitic form, specially during the epidemic period. Psychic disorders occurred in 25 per cent of cases of encephalitic Parkinsonism, and in 10 per cent of cases of paralysis agitans, usually in association with involutional changes. Disturbance of sleep rhythm was restricted to encephalitic Parkinsonism.

Differing views regarding the course and prognosis of encephalitic Parkinsonism and paralysis agitans have been expressed by various writers. Wilson (1940) and Collier and Adie (1941) considered that there was a tendency to arrest, if not amelioration, in encephalitic Parkinsonism, whereas paralysis agitans showed a progressive downward course. Brain (1940) stated that the course of Parkinsonism following encephalitis is usually more rapidly progressive than that of paralysis agitans. In the cases under consideration, the course of encephalitic Parkinsonism judged by duration of symptoms was shorter than that of paralysis agitans during the epidemic years, but more prolonged in the 1931 to 1942 group. The longest latent period between the causative attack of encephalitis and the development of Parkinsonism was 19 years. To summarize, encephalitic Parkinsonism during 1920 to 1930 differed from paralysis agitans in degree of rigidity and salivation and in the presence of additional signs and symptoms, notably oculogyric crises, multiple abnormalities of ocular movements and pupillary function, psychic disorders, and disturbance of sleep rhythm. During 1931 to 1942 the course of encephalitic Parkinsonism became more prolonged, and the differentiating clinical features less marked. This approximation of encephalitic Parkinsonism to paralysis agitans may have a pathological basis. Jakob (1925) and Alexander (1942) have suggested that the acute and subacute processes of epidemic encephalitis bring about changes in the basal ganglia which, often practically recovering from the infiltrative and inflammatory components, go on to a progressive nuclear degeneration. The final result of milder encephalitic infections might, therefore, be indistinguishable from paralysis agitans.

3 The term indeterminate Parkinsonism has been used in the present paper for a group of cases foreshadowed in 1920 to 1930, but occurring principally during 1931 to 1942. These resembled subacute Parkinsonism of the epidemic period in moderately rapid onset, rigidity, eye-signs, and sleep disorders. An unequivocal history of encephalitis was lacking, although

the substantia nigra, and the presence of residual inflammatory changes. Although in longstanding cases the perivascular infiltration and diffuse glial proliferation may resolve, some adventitial fibrosis and coarseness and irregularity of glial fibrils usually persist. The diagnostic lesions in syphilitic vascular Parkinsonism are stated to consist of proliferation of the vascular endothelium, and an infiltration of lymphocytes and some plasma cells in the adventitia and perivascular spaces. In the Jakob Creutzfeldt syndrome atrophy of the corpus striatum is associated with severe atrophy of the cerebral cortex and degeneration of the corticospinal fibres. The pathological conception of idiopathic Parkinsonism (paralysis agitans) as a presenile degenerative disorder is supported by the characteristic age distribution of the disease tabulated by Souques (1921), Patrick and Levy (1922), and Wilson (1940). The present series also showed a consistent modal age of onset in the sixth decade for cases which in other clinical features resembled classical paralysis agitans.

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group of encephalitic Parkinsonism Mental symptoms and eye signs were unchanged in incidence The approximation of encephalitic Parkinsonism to paralysis agitans tends to support Jakob's view that sublethal damage to the ganglion cells by a virus results in their degeneration at deferred intervals Forty-two cases of indeterminate Parkinsonism showed an age distribution suggestive of an aetiological factor incident in young people in the years corresponding with the epidemic of encephalitis lethargica The common identity of these cases with encephalitic Parkinsonism was confirmed by the frequent presence of sleep disorders and eye signs Rigidity was prominent in this group as in Parkinsonism of acute onset in the epidemic years There appeared a definite left sided predominance of signs, which was difficult to explain Over the whole group the age of incidence was increasing, but the onset of symptoms was frequently associated with sleep disorder or a minor febrile illness The duration of symptoms appeared shorter than in the current declared type of encephalitic Parkinsonism These discrepancies may perhaps be attributed to the activity of a cryptogenic infection which after a period of latency destroys the affected ganglion cells, producing Parkinsonism resembling in type that of the previous decade in fairly rapid onset and predominance of rigidity It is improbable that these cases are the result of a fresh infection of subclinical encephalitis occurring after the subsidence of the epidemic wave, because of the relatively late age of onset One case of Parkinsonism and syphilis, and a case of the Jakob-Creutzfeldt syndrome complete the series

I wish to express my thanks to Dr Riddoch for valuable criticism My thanks are due to the members of the Honorary staffs of University College Hospital and Maida Vale Hospital for Nervous Diseases for permission to use case records past and present I am specially indebted to Dr Russell Brain, at whose suggestion the paper was written, for much helpful advice and access to his clinical records

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a minor febrile attack in some cases preceded the development of symptoms. In contrast to encephalitis lethargica which predominately attacked adolescents, these cases occurred in progressively later age groups with the passage of time since the epidemic period. Such a clinical course might be explained by the hypothesis that activation occurs of a prior virus infection of the ganglion cells acquired during the epidemic period. Modern views are tending to attribute to virus infections the capacity of remaining dormant for lengthy periods in cells.

### *Conclusions*

*1900 to 1919* (One hundred cases) The majority of cases of Parkinsonism attending for treatment during these years were cases of paralysis agitans. The symptoms developed in the second half of life, with the modal age of onset occurring between 51 to 60 years of age. The duration of symptoms in over half the cases did not exceed two years. The chief symptom and objective sign was tremor, affecting the right side of the body. Abnormal mental states were rare and restricted to the older patients. Excessive salivation was uncommon, and the ocular movements and pupillary reactions were usually normal. Three juvenile and two senile cases were recorded.

*1920 to 1930* (One hundred cases) Thirty-four cases resembled the previous group of paralysis agitans in most of their clinical features. There was an increased recording of ocular anomalies, chiefly weakness of convergence. Fifty-four cases resulted from an attack of encephalitis lethargica, and the sequelae were usually immediate. A large proportion of these cases (72 per cent) sought medical advice within two years, showing a severe degree of Parkinsonism of rapid development. Mental symptoms and disorders of sleep were common. Shakiness was the usual presenting symptom, but rigidity appeared more prominent on objective examination, and the distribution was general with a right sided predominance. The incidence of excessive salivation was high. In most cases eye signs, consisting of abnormalities of external ocular movement and pupils, complicated the Parkinsonism. The common defect was failure of the pupil to contract on accommodation, but was almost invariably associated with other ocular abnormalities. Eleven cases classified as indeterminate Parkinsonism resembled encephalitic Parkinsonism in clinical form, but differed in the absence of a history of encephalitis. There was one case of Parkinsonism and neurosyphilis.

*1931 to 1942* (One hundred and twenty cases) Fifty-two cases fall into the group of idiopathic Parkinsonism (paralysis agitans) conforming in age distribution, duration of symptoms, and objective signs with the classical type. Twenty-four cases of encephalitic Parkinsonism in this series were characterized by a long latent period, or prolonged duration of symptoms. The onset of symptoms had become gradual and tremor was predominant as in paralysis agitans, whereas rigidity was less marked than in the previous

# CRANIOFACIAL DYSOSTOSIS THE SIGNIFICANCE OF OCULAR HYPERTELORISM<sup>1</sup>

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(From the Royal Infirmary, Glasgow)

With Plates 12 to 15

## *Introduction*

NUMEROUS attempts have been made from time to time to group together the developmental abnormalities which involve the skull and facial bones. These attempts were based on clinical descriptions and anatomical studies made *post mortem*, and there has been a tendency to accept clinically distinct anatomical defects as separate pathological entities. Even with the added means of investigation provided by radiology, there has been little or no clarification of the subject. The emphasis has been laid on differentiation, with an elaboration of nomenclature, in a group of conditions which often have many features in common, and are best included in the category of craniofacial dysostosis. The following are the chief types of craniofacial dysostosis differentiated up to the present time.

*Oxycephaly* This condition is characterized by excessive growth of the skull in a vertical direction. The frontal and bregmatic regions are prominent and the anteroposterior diameter is short. It is accompanied usually by shallow orbits, exophthalmos, and a beak-like nose. The deformity is regarded as due to premature closure of the coronal suture. *Acrocephaly* has been described as a variant of this condition, the skull being truncated, as distinct from the bullet-shaped appearance in oxycephaly.

*Scaphocephaly* Elongation of the anteroposterior diameter is the essential feature and sometimes the vault is keel-shaped. Premature closure of the sagittal suture is thought to be the cause. The parieto-temporal, spheno-parietal, and spheno-temporal sutures may also be involved. Frequently the posterior fossa is enlarged and overhangs the base of the skull. Brachycephaly with undue prominence of the bregmatic region, and dolichocephaly with a prominent frontal region, are variants which lie between oxycephaly and scaphocephaly.

*Plagiocephaly* The skull is asymmetrical about the sagittal suture. This may result from premature closure of one or more sutures on one side, with consequent overgrowth on the other. It may be due to hemiatrophy of the brain, when the skull may be thickened on the affected side. Various other sutures may be involved, resulting in some modification of the essential

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The palate is often highly arched and narrow, and the gums hypertrophic, but alterations in the shape of the mandible sufficient to cause disability, as in Case 3, are uncommon. Deformities elsewhere in the body are sometimes present, and those most commonly encountered are hernia, undescended testes, and anatomical defects in the hands and feet (see Table). Affection of the higher nervous and mental functions is variable, and does not always occur in proportion to the degree of deformity. Pickerill (1938) reported the mental state of his first case as brilliant and his remaining four cases were

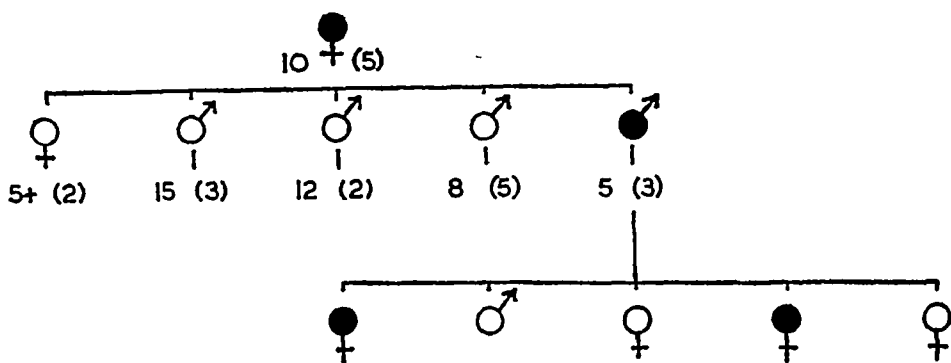


FIG 1 Family No 1 Numbers indicate size of family in each instance. Numbers in parentheses indicate those surviving to adult life. Affected individuals are shown in black.

of normal mentality. The disposition of those mentally affected is usually even-tempered and gentle. In the majority of cases hitherto recorded there is no history of hereditary transmission. It was sought in most cases, and those in whom it was noted are indicated in the Table. Günther's (1933) belief that a hereditary element is lacking is thus not confirmed.

#### *Personal Observations*

The cases to be described comprise two families, each affected in at least three generations. In the first family the deformity resembled, though only in part, that described by Greig, in the second hypertelorism was associated with oxycephaly.

*Family No 1* This family consisted of father, mother, and five children, four girls and a boy. The father and the first and fourth children were affected. The father's mother had also been affected (Fig 1). A remarkable feature of this prolific family was the high mortality at an early age. Of at least 55 persons in two generations, only 20 reached adult life. There was no history of consanguineous marriage.

*Case 1*, a healthy, muscular quarryman, aged 64 years, presented a marked degree of hypertelorism (Plates 12 and 13, Figs 3, 4, 5, and 6). No history of his youth was available, but on examination he was found to be mentally dull and illiterate. He was even-tempered and of quiet disposition. Bilateral deafness had been present for as long as he could remember. It appeared to

deformity Plagioprosopia indicates asymmetry of the face, it is associated usually with cranial asymmetry Case 5, to be described, illustrates this type of deformity

*Trigonocephaly* Maldevelopment of the frontal region, and excessive development of the posterior part of the skull, are the essential features of this deformity Premature closure of the coronal sutures is regarded as being responsible

*Platycephaly* This defect is characterized by enlargement of the posterior fossa, which overhangs the cervical spine with the result that the latter appears to be invaginated into the skull The deformity is thought to be due to premature closure of the sutures of the vault, with overgrowth at the occipito-parietal suture A similar type of deformity may be produced by the occurrence early in life of softening of the skull bones, for example in rickets

*Craniofacial dysmaturity* This deformity has been regarded as due to premature closure of many sutures, which leads to gross alterations in the skull, often associated radiologically with marked 'thumbing' of the skull

*Hypertelorism* This is a descriptive term applied to a craniofacial deformity associated with undue separation of the orbits The condition is considered in greater detail below, with special reference to two families in each of which a hereditary element was evident

#### *Ocular Hypertelorism*

The term hypertelorism was first used by Greig (1924) to describe undue orbital separation, the antithesis of cyclopia, or single mid-line orbit Hypertelorism was the salient feature in a craniofacial defect which he regarded as due to abnormal development of the lesser wings of the sphenoid bone Overgrowth of these was found to be associated with a persistent cranio-pharyngeal canal containing the nasopharyngeal stalk of the pituitary Subsequent reports on this deformity are not numerous, but they suffice to show clearly that all cases with undue separation of the orbits do not necessarily show similar changes in the sphenoid bone Hypertelorism is remarkable not only in the type of skull deformity with which it may be associated, but also in the variety of abnormalities in the bones and soft tissues which frequently accompany it A detailed account of these, obtained from a review of available literature, is presented in the Table Hypertelorism is usually bilateral, but asymmetry and even a completely unilateral deformity may occur (Lightwood and Sheldon, 1928, Divry and Evrard, 1935) The deformity is often accompanied by great breadth of the nasal bridge, the bones of which may be massive Occasionally the bridge is depressed and the nose retroussé, or the tip may be retracted and distorted (Pickerill, 1938) Even with flattening of the nasal bridge, the hypertrophic nasal bones limit the fields of vision on the nasal side Ocular movements may be poor, and even in the absence of strabismus binocular vision may be considerably impaired, particularly for close objects The mouth frequently shows some abnormality

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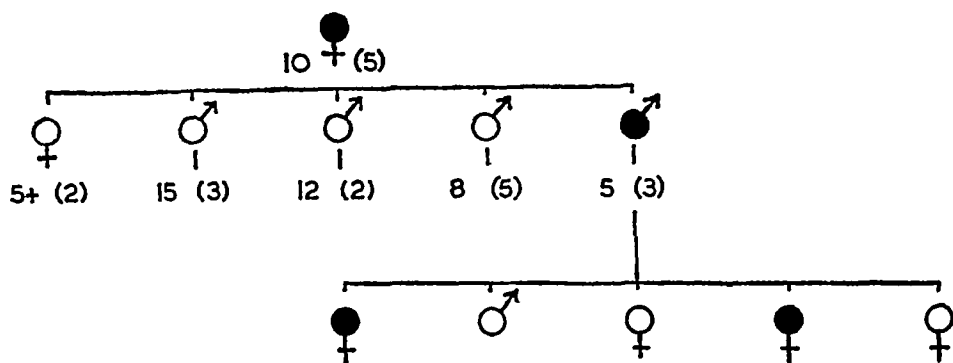


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Author	Number of cases	Heredit	Mental defect	Other defects	Radiological appearances
Greg (1924)	2 a b	— —	— —	Strabismus Unable to close mouth	— Normal shape of skull, poor antra and ethmoids, no frontal sinuses
Cockayne (1925)	2 a b	— —	+ —	Undescended testis Abnormal ears and fingers	High skull, flat occiput Whole skull not shown
Muir (1925)	1	—	+	Arched palate, hernia, deformity of ears	? Congenital facial cleft
Allen (1926)	1	+	—	Strabismus, undescended testis	Round orbits, wide ethmoids
Braithwaite (1926)	1	—	—	Arched palate	Brachycephaly
Drummond (1926)	1	—	+	Arched palate	None given
Abernethy (1927)	1	+	—	Ptosis, nystagmus, strabismus, palate narrow and arched, hernia, webbed toes	Deformity of sphenoid
Ogilvie and Posel (1927)	3 a	—	—	Webbed toes	Poorly developed sphenoid, no frontal, maxillary, and sphenoid air cells, bones thin
Symonds (1927)	b	+	—	—	Oxycephaly
Babonneix, Lamy, and Delarue (1928)	c —	+	—	—	Not given
Jansen (1928)	1	—	+	Strabismus, per canthus, ectopic testis	Not given
Lightwood and Sheldon (1928)	1	—	—	Acrocephaly, syndactylia	—
Montford (1929)	1	+	—	Webbed toes, strabismus	Unilateral deformity, prominent right temporal region
Rawson and Avila (1930)	1	—	—	Genu valgum, hernia	Bones of skull thin (No film shown)
Regnault and Crouzon (1930)	2 a b	— —	—	? Congenital facial cleft	Very poor X-ray reproduction, large sinuses
Reilly (1931)	4 a b	— — —	— — —	Strabismus Strabismus Sprengel's deformity, elevated palate, bifid uvula	No radiographs
				Arachnoidecty and webbing, strabismus	—

	c	+	+	Strabismus, ? congenital heart disease, thumbs abnormal	Enlarged thumbs, terminal phalanx of thumb and toe increased in width
	d	—	—	Strabismus, congenital heart disease	—
Whitwell (1931)	1	—	—	Rudimentary nails, skin dry	None given
Chotzen (1932)	3	—	One family	—	Turriccephaly, no mastoid cells or frontal sinuses
	b	—	—	Syndactyl, erythrehidism	Turriccephaly, plagiocephaly, no mastoid cells or frontal sinuses
	c	—	—	As b	Similar to case b
Cowan and Silberman (1933)	4	—	In one family	Not described in detail	—
	a	—	—	None	—
	b	—	—	None	—
	c	—	—	None	—
	d	—	—	Strabismus	—
Gunther (1933)	2	—	—	(A very mild case)	—
	a	—	—	(A very mild case)	—
Kruger (1933)	1	—	—	Strabismus, deaf and dumb	None given
Tozer (1933)	1	+	—	Epilepsy, genu valgum, strabismus	Thickened skull, evidence of increased intracranial pressure
Allen (1933)	1	+	—	Strabismus, large ears, deformity of hands, and disproportion in trunk and legs	Hypertrophied body of sphenoid, large greater wings
van Bogaert and Sweerts (1935)	2	?	—	Spastic paraplegia, epilepsy	Hypertrophied body of sphenoid, absorption of anterior clinoid processes
	b	+	—	Petit mal, strabismus, clavicle deformed, elevated palate	Large sphenoidal sinuses more marked on right Metopic suture
Davry and Evrard (1935)	1	Slight	—	Divarication of recti	Large lesser wings of sphenoid
Kersley (1935)	2	—	—	Fragilitas ossium, kyphoscoliosis	Large lesser wings of sphenoids, sclerosis of mastoids
	a	—	—	Redundant soft parts in mid-line of face	Poor radiographs
van Voorthuysen (1935)	1	—	—	Sprengel's deformity, hernia, genu valgum, talpes valgus, pes planus	None given
Slo Bodkin (1936)	1	—	+	—	—

Author	Number of cases	Hereditary	Mental defect	Other defects	Radiological appearances
Touraine, Solente, and Viollette (1936)	1	—	—	—	Asymmetrical defect, conical vertex, nasal bones and maxilla small, mandible large with no coronoid processes
Bojlen and Brems (1938)	11	In five generations	—	Autopsy one case revealed hypertrophy of lesser wings of sphenoid	—
Deutman and Kenzer (1939)	1	—	—	—	Thick cranial bones
Oldfield (1937)	1	—	—	Encephalocoele, cleft palate	Defect in sphenoid
Reuben and Fox (1938)	1	+	+	Strabismus, myopia	—
Pickorill (1938)	3	—	—	—	—
	a	—	—	—	—
	b	—	—	—	—
	c	—	—	—	—
Reubens (1939)	2	—	—	—	Plagiocephaly.
	a	—	—	—	—
	b	—	—	—	—
Berliner and Gartner (1940)	1	—	—	High palate	—
	1	—	—	Elevated palate	—
Posner and Platt (1940)	1	—	+	Cleft palate, hare lip, giant cell tumour of femur	Large sinuses, enlarged sphenoidal fissures
Vorsek (1941)	4	—	—	Congenital dislocation of hip, webbed digits	Enlarged lesser wings of sphenoids
	a	—	—	—	Large lesser wings of sphenoid ( <i>post mortem</i> )
	b	—	—	—	—
	c	—	—	Strabismus, undescended testis	—
	d	—	—	Congenital glaucoma	—

be of nerve origin, but localization was difficult owing to lack of co-operation. The only physical defect was in the skull. The orbits were widely separated.

Distance between inner canthi—4.7 cm (Normal about 3 cm)

Distance between outer canthi—9.6 cm (Normal about 9 cm)

*X-ray appearances* The skull was unusually thick and large with the thickening most marked in the basi-occiput, and sphenoidal and frontal areas. The bony texture was coarser than usual, but except in the frontal and parietal areas the inner and outer tables could be differentiated, and vascular channels could be distinguished. The sutures were all closed and marked sclerosis along all their lines of fusion was evident. The sella turcica was of normal size, but the sphenoidal ridges were unusually high. The orbits were far apart, and rather oval and oblique. The frontal and maxillary sinuses were absent, and the mastoid areas dense and acellular. Coarse ethmoidal cells of considerable extent occupied a much wider area of the interorbital region than is normally seen. The sphenoidal sinuses were present. The maxillae and mandible were heavier and coarser than usual and the nasal bones were much denser and also beak-shaped. The sphenoidal fissures were narrow and the optic foramina normal in size but oval in shape. The mentovertebral view of the skull showed no abnormality in the fissures or foramina of the base. Examination of the rest of the skeleton showed only a certain heaviness and coarseness of the bones similar to that seen in the skull, but with no other significant features.

*Case 2*, the eldest daughter, aged 35 years, showed a marked degree of hypertelorism (Plate 14, Fig 7).

Distance between inner canthi—5.3 cm

Distance between outer canthi—10.1 cm

There was also hypertrophy of the nasal bones, flattening of the nasal bridge, and slight deafness of nerve origin. The palate, uvula, and gums were normal. Ocular function was unaffected. Inquiry into her early years revealed that shortly after birth it was noted that the nose was short and that there was nasal obstruction. Development in infancy and childhood was retarded. She was sent to a school for mental defectives, and at the age of 16 years she was able to read a little, write her name, knit, and sew. At the age of 27 years she gave birth to an illegitimate child. Whether the child showed any developmental abnormality is unknown.

*X-ray appearances* There were no essential differences in the appearances of this patient's bones as compared with those of her father. The ribs, clavicles, pelvis, and other bones exhibited a certain coarseness and heaviness unusual in a woman of her size and age.

*Case 3*, aged 20 years, was the fourth child of the family. She had been born without difficulty and during infancy and childhood had shown only slight evidence of retarded development. From infancy it had been noted that she was unable to bring her front teeth into apposition. Slight nasal obstruction had been present from an early age. When seen, she was a well-built, muscular young woman. No deformity was present elsewhere than in the head and face, and hypertelorism was marked (Plate 14, Fig 8).

Distance between inner canthi—5.5 cm

Distance between outer canthi—10.8 cm

The deformity was associated with a massive nasal bridge which produced great limitation of visual fields on the nasal side. The gums, especially in the upper jaw, were hypertrophic. The mouth was so distorted that apposition of the gum margins in the mid-line was impossible. A gap of almost



1.5 cm remained. The lower jaw was massive, and the palate very narrow and highly arched. Mentally she was slightly subnormal. Speech was indistinct and the words ill-formed. No radiographs could be obtained as the patient would not submit to X-ray examination.

*Family No. 2* Three members of this family, belonging to three generations, were affected (Fig. 2). Only two were examined. The father's mother had been the first case noted in the family. She had attributed her unusual facial

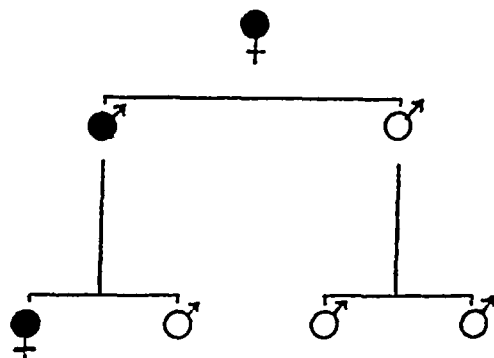


FIG. 2. Family No. 2. Affected individuals are shown in black.

appearance to intra-uterine injury. There was no history of consanguineous marriage in this family.

*Case 4*, aged 49 years, was a well-built, rather spare man of average intelligence. His only physical defect was in the head and face. A moderate degree of hypertelorism was present (Plate 15, Fig. 9).

Distance between inner canthi—4.3 cm.

Distance between outer canthi—9.5 cm.

The gums, palate, and uvula were normal.

*X-ray appearances.* Radiological examination revealed a scaphocephalic skull, the bones of which possessed a normal texture. The orbits were widely separated. The ethmoidal sinuses were coarse and unusually extensive, but the mastoid processes were acellular.

*Case 5*, aged 18 years, was a poorly nourished girl with very slender bones and a small round head (Plate 15, Fig. 10). She showed a marked degree of hypertelorism.

Distance between inner canthi—5.2 cm.

Distance between outer canthi—10.7 cm.

The nose was retroussé. The head was small and rather spherical, with flattening in the left frontal and supra-orbital regions. Apart from the presence of decayed teeth, the gums were normal. The palate was narrow and highly arched. Although ocular movements were full, convergence was incomplete and binocular vision much impaired, specially for close objects. Associated deformities comprised a scoliosis with prominence of the right side of the chest posteriorly. The middle third of the right clavicle was defective, giving rise to weakness and undue mobility in the right side of the shoulder girdle. No history was given by the father of delayed development of his daughter in infancy. Both osseous defects had been noted at birth. She

attended school from the age of five years, and apparently made normal progress in spite of defective vision. For some years she had tended to suppress the image in the right eye. On examination, a considerable degree of mental defect was found to be present.

*X-ray appearances* The skull exhibited many interesting features. There was oxycephaly associated with plagiocephaly (asymmetrical skull) and plagioprosopia (asymmetrical face), as well as a marked degree of ocular hypertelorism. The oxycephaly is in strong contrast with the scaphocephaly shown by the father (Case 4). The left petrous bone was higher than the right, a feature probably related to the plagiocephaly. The face was small, but all the paranasal sinuses, including the ethmoidal and sphenoidal, were well developed. The mastoid processes were cellular. The nose showed slight deviation to the left side. The middle third of the right clavicle was represented by a band of dense fibrous tissue. The right scapula was smaller than the left and rotated into an abnormal position. The coracoid process was bifid with an additional distal projection. The left clavicle had a concave inferior surface above the coracoid process, which was enlarged and had produced a pressure defect on the clavicle. Apart from the very small thorax and the slender ribs, which were in keeping with the build of the patient, no further abnormalities were observed. Further examination was prevented by the patient's death soon after operation for an appendix abscess for which she was primarily admitted to hospital.

#### *Discussion*

Throughout the literature on hypertelorism there has been a tendency to accept the ocular defect as the fundamental abnormality. It is evident from the reports reviewed and from the cases described in the present series that the undue separation of the orbits may reflect one of several basic changes. Greig's (1924) original cases showed overgrowth of the lesser wings of the sphenoid bone. Similar changes were described by Kersley (1935), Posner and Platt (1940), and Vorisek (1941). The two cases reported by van Bogaert and Sweerts (1935) showed hypertrophy of the body of the sphenoid, and in the first, the greater wings of the bone were also enlarged. Oldfield (1937) described hypertelorism associated with an encephalocele which protruded into the nasopharynx through a defect in the anterior part of the body of the sphenoid. The cases of Muir (1925) and Rawson and Avila (1930) may have been due to persistence of the facial cleft. Great variation has been recorded in the radiological appearance of the skull. Unusual thickening of both skull and mandible was present in the cases described by Ogilvie and Posel (1927, Case 2), Touraine, Solente, and Vialatte (1936), and Deutman and Keizer (1939). Greig (1924) commented on the radiological appearances suggesting an unusually thick vertex in his second case, but this was not confirmed at autopsy. In our own series thickening to an extreme degree was seen in all three cases of Family No. 1. In addition, the exact similarity of the skulls of the father and daughters, the great density, the absence of air cells except the very coarse ethmoid cells, and the general coarse texture of the bones form a group of features which has not previously been described. The skulls of Family No. 2 (Cases 4 and 5) are quite different from those of

Family No. 1 and in addition they are different from one another. This is not uncommon in hereditary abnormalities and a deformity may vary from generation to generation, a feature well illustrated by Brailsford (1945) in his study of familial brachydactyly. Since hypertelorism is symptomatic of a growth defect in the skull, the question of the aetiology of the undue ocular separation defect is fundamentally that of the defect in the primitive mesoderm, development of which tends to be associated with structural abnormalities involving chiefly, but not only, the bones of the skull. The mechanism by which the defect produces distortion of the shape of the skull has been discussed by Isola (1932), who regards premature closure of one or more sutures as the chief factor in the production of the many types of craniofacial dysostosis already described. In reviewing the radiographs available both in the literature and from the patients in the present series, it is evident that in the majority the sutures are not obviously abnormal. This does not necessarily vitiate Isola's hypotheses, because the union of sutures may commence in the diploë and spread to the inner and then to the outer table. Thus when a deformity is present, functional closure of sutures may coexist with apparently normal serrations of the outer table shown radiologically.

### *Summary*

1. The clinical features and radiological appearances in five cases showing ocular hypertelorism are described, and the available literature on the subject is reviewed.

2. It is emphasized that ocular hypertelorism is a descriptive term without aetiological implication, and that it is a condition which may occur with any type of craniofacial dysostosis.

3. Ocular hypertelorism is an abnormality which is evident in infancy and persists throughout life. The majority of affected subjects suffer from strabismus, defective visual fields, and defective binocular vision. About one in five show definite mental defect, which, however, is not always related to the degree of the deformity, and half the cases have some additional physical defect.

4. The aetiology of the various types of craniofacial dysostosis is unknown. Premature closure of sutures may be responsible, but this is not always demonstrable by radiology.

The authors wish to thank Dr David Smith for permission to study Case 2 and Mr G. T. Mowat for the introduction to Case 5.

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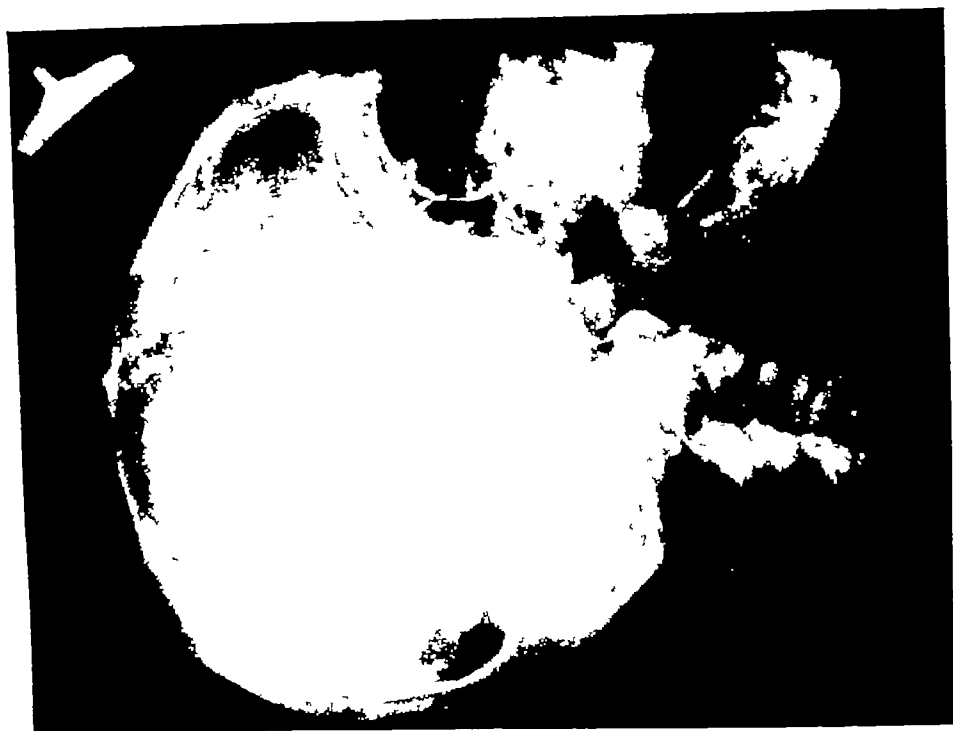


FIG. 3



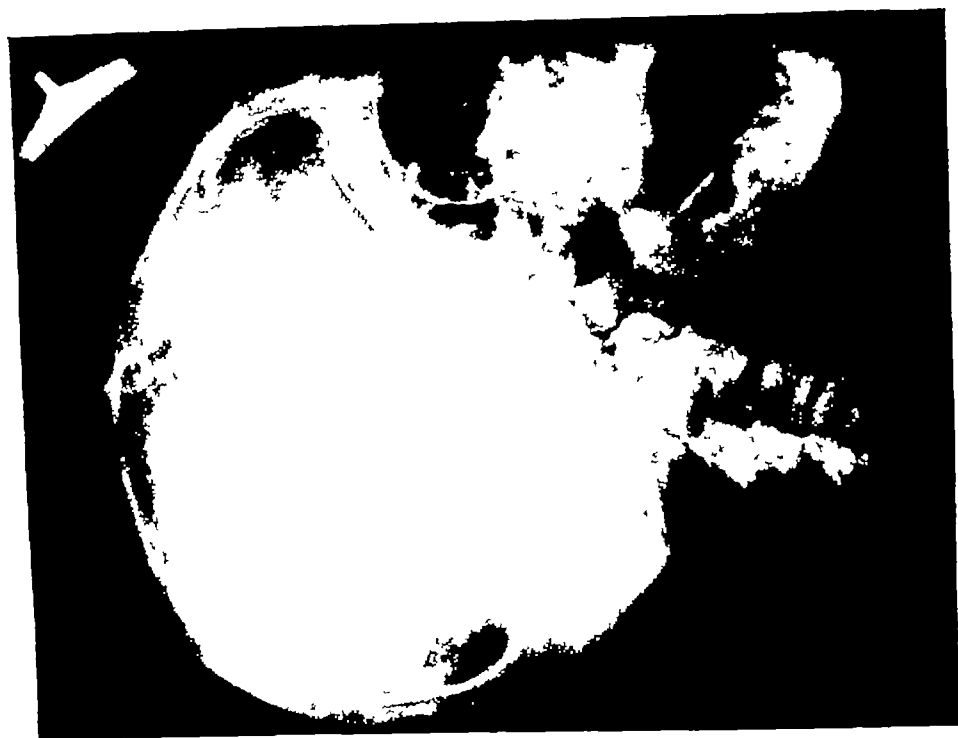


Fig. 4



Fig. 3







Fig. 6



Fig. 5





FIG 7



FIG 8



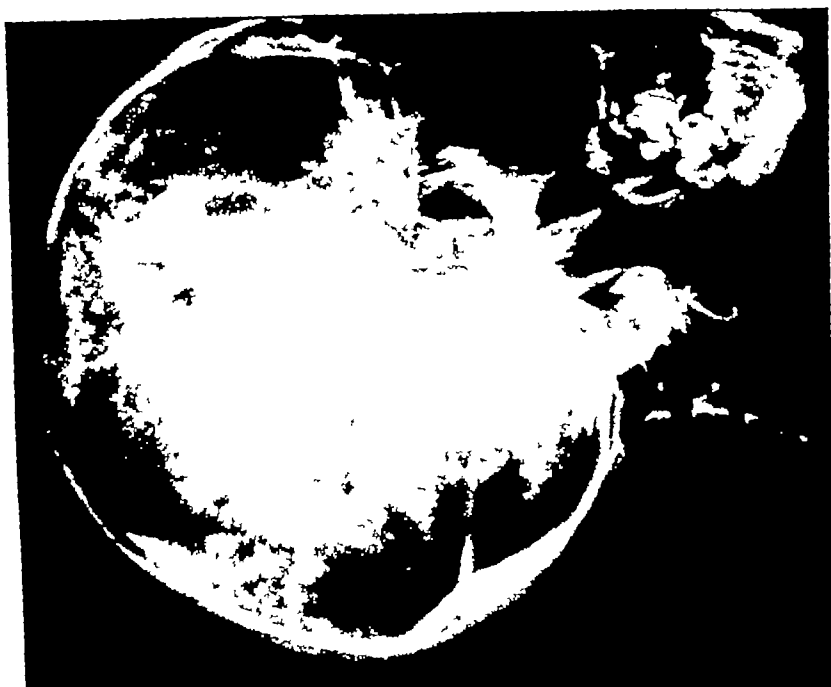


FIG 10

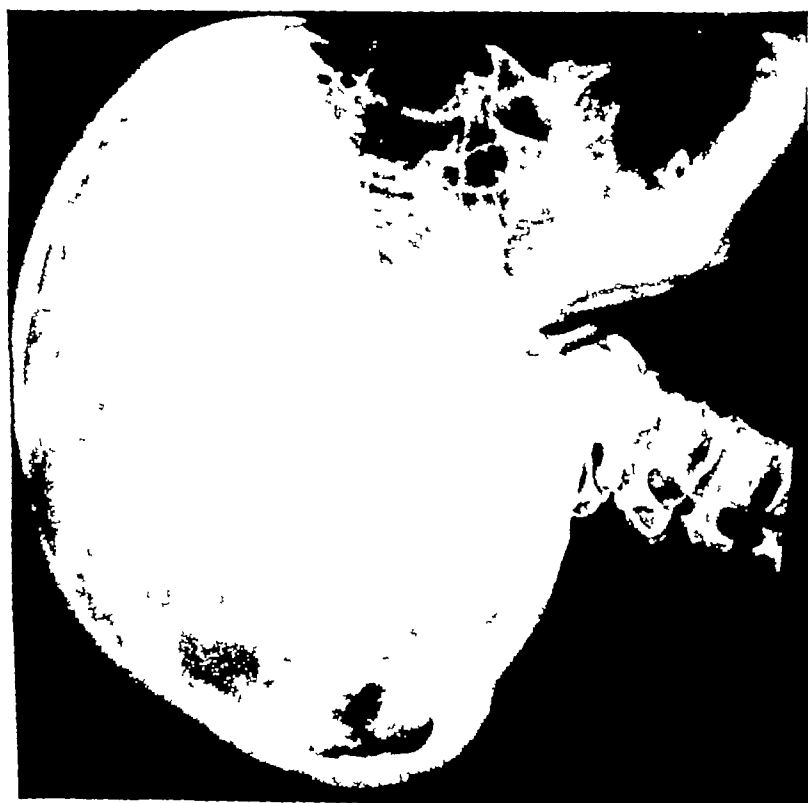


FIG 9



## THE EPIDEMIOLOGY OF THE 1945 OUTBREAK OF POLIOMYELITIS IN MAURITIUS<sup>1</sup>

By A M McFARLAN, G W A DICK, AND H J SEDDON

### *Introduction*

DURING the month of March 1945 there were about 800 cases of poliomyelitis in the island of Mauritius, and over 1,000 cases occurred during the first five months of the year. The attack rate was 2.4 per 1,000, so that the outbreak was comparable in intensity with the 1916 epidemic in New York (Lavinder, Freeman, and Frost, 1918) and the 1942-3 outbreak in Malta (Seddon, Agius, Bernstein, and Tunbridge, 1945). The presence of an epidemic was recognized by the Department of Medicine and Health at the beginning of March, with the assistance of a corps of V A D s a search for cases was made and it was found that they were widely distributed. The schools were closed and children prohibited from travelling in trains or buses. Soon after April 15, the date of our arrival in Mauritius, the Government Medical Officers prepared lists of cases in the nine districts giving the date of onset when known. From these lists it appeared that the epidemic had begun during February in Rosehill, had spread all over the island in March, and was practically at an end by the third week in April.

### *The Island and its Population*

Mauritius is situated in the Indian Ocean, 600 miles east of Madagascar and 20 degrees south of the equator, at the southern limit of the tropics. The island (Fig 1) measures some 38 miles from north to south and about 28 miles from east to west. In the low-lying northern part are the districts of Pamplemousses and Rivière du Rempart, mainly devoted to sugar production but with a few fishing villages, and a considerable number of market gardens in Pamplemousses. The southern parts of these districts rise to the central plateau with its encircling ranges of mountain peaks rising to about 2,000 feet. At the south-west corner of Pamplemousses is the district of Port Louis, with the capital town of the same name lying between the harbour and the surrounding hills. From Port Louis the main road and railway go south and west to the central plateau through the towns of Beau Bassin, Rosehill, and Quatre Bornes in the district of Plaines Wilhelms. Higher up are Phoenix, Vacoas, and Curepipe surrounded by sugar estates. Beyond Curepipe there is uncultivated woodland in the hills and then several straggling villages among sugar estates on the way down to the small town

<sup>1</sup> Received January 25, 1946



of Mahébourg in the district of the Grand Port. From a fork south of Cure pipe a branch road leads south-west to the sugar estates and fishing villages in the district of Savanne. From Port Louis and Rosehill other roads go to sugar estates in the districts of Moka and Flacq in the eastern part of the

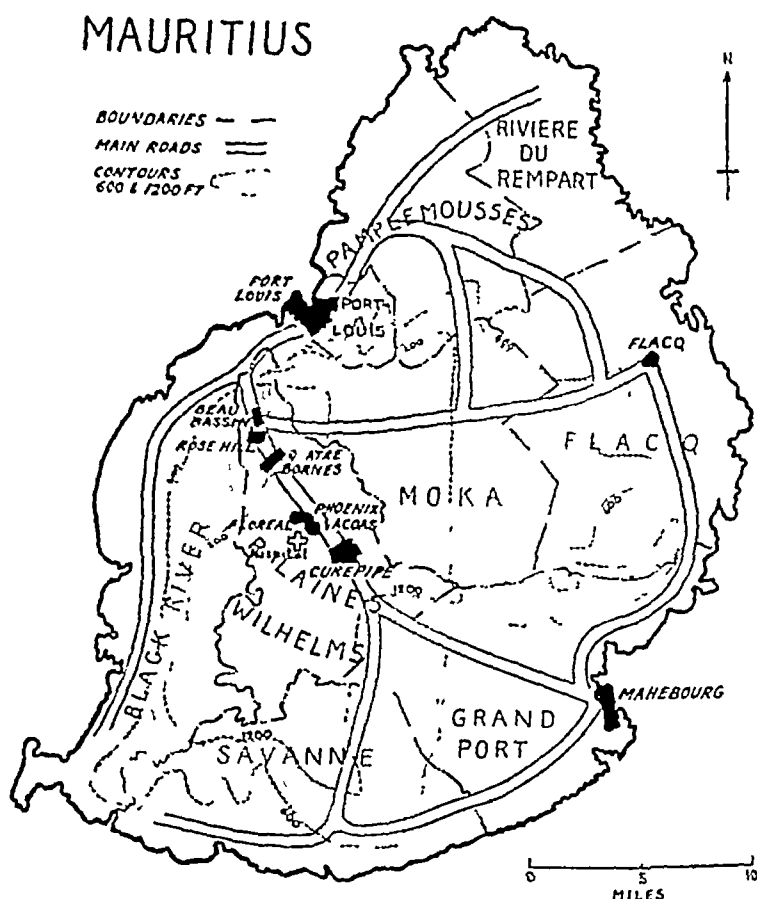


FIG 1 Map of Mauritius

island, and others to the mountainous, sparsely populated district of Black River in the south-west.

**Climate** The mean temperature in the midsummer month of January is 78° F on the coast and 75° F on the central plateau, corresponding temperatures in July, the coldest month, are 68° F and 64° F. Rainfall varies from 45 inches a year on the coast to 148 inches in the hills. The wettest months are December to April. In 1944 August and November were very dry. In September, October, and December 1944 and January 1945 the rainfall was above the averages for these months, while in February and March 1945 the fall was less than the average. Three cyclones hit the island in 1945, on January 15, February 2, and April 7. The first two caused damage all over the island, the third affected mainly the south-eastern part.

*Housing* Most of the houses are bamboo huts with thatched roofs and mud floors, there are also stone and wood huts, some with corrugated iron roofs, while a few well-built wood or concrete houses are occupied by the wealthier people. Overcrowding in Mauritius is very great, as was shown by the 1944 census (Table I). It is particularly marked in Port Louis where only the poorer classes live, wealthier people come in daily to work, and live in higher

TABLE I  
*Overcrowding*

Percentage of families with three or more persons per room			
1944 census figures		1938 census figures	
Mauritius	27.9	England and Wales	3.1
Port Louis	49.1	Stepney	8.4
Curepipe	19.5	Hampstead	0.2

and less malarious districts. The towns of Beau Bassin, Rosehill, and Quatre Bornes are crowded with poor people, Vacoas and Phoenix have some better houses, but also many crowded slum areas, and Curepipe similarly presents a patchy elegance. In the villages the houses are spread out along the roads or scattered irregularly over the hill-side or along the coast. On some sugar estates there is the same haphazard arrangement of houses as in the villages, in others there are barrack rows of bamboo or stone huts. The cyclones intensified overcrowding during the early months of 1945. Families had to share houses or were herded together in halls and schools. The schools are poorly built, ill-ventilated, and far too small for the number of children attending.

*Sanitation* The sanitary arrangements are poor all over the island. Port Louis is the only place with a water-carriage system, Curepipe has bucket latrines. Most places have unscreened pit latrines with rickety superstructures. Many of these were blown down by the cyclones, and until repairs were carried out weeks or months later the latrines were used even less often than usual. Refuse lies in heaps in the streets and yards of towns, villages, and sugar estates.

*Diet* The diet of the majority of the population is very poor by European standards, protein in particular being deficient. Meat is rarely eaten because it is so scarce and fish is seldom available. Milk is frequently adulterated and so scarce that children receive it only in tea or milk puddings, it is always boiled before use. Before the war the main article of food was rice, but during the war it became scarce so that flour and vegetables were the staple diet. After the cyclones vegetables were almost unobtainable. The poverty of the diet was increased among the poorer classes by a 'black market' which raised prices far above their means. In spite of the inadequacy of the diet it did not appear that malnutrition determined the incidence of poliomyelitis. The patients seemed to be at least as well nourished as other members of their families who escaped the disease, and there was a high incidence in Chinese children who enjoyed a more abundant diet than Indian and Creole children.

*Population* A census taken on June 11, 1944, showed that the population numbered 419,185. More than half (205,247) were Indians, who are the descendants of indentured labourers and form the main labour force on the sugar estates. Three quarters of them are Hindus and one quarter Moslems. The latter are mainly town-dwellers, engaged in trade. In the 'general population' (143,056) Creoles predominate, they are descendants of the slave population and are of African or Malagasy origin. There are many people of mixed race, and relatively few white Mauritians, mostly of French origin, with a sprinkling of British people. The Chinese number 10,882, and are almost all shopkeepers.

*Prevalent diseases* Malaria is prevalent in the coastal districts. Ankylostomiasis is widespread. Enteric fever is endemic and there was an epidemic in the village of Triolet in Pamplemousses in 1944-5. Amoebic dysentery is apparently increasing. Poliomyelitis is endemic. A few cases have been notified from time to time since 1927, when the disease was made notifiable, and a considerable number of old cases were seen clinically, one dating from 1891.

#### *Method of Field Survey*

An exhaustive questionnaire (see Appendix) was drawn up for recording the clinical and epidemiological details of cases. It was modelled on that used by Frost (1941). After recording identification data, the dates of onset of symptoms were entered on a list. In all accessible cases the results of clinical examination were also recorded. These findings were used to decide whether the case was one of poliomyelitis or not, and in accepted cases to fix the date of onset. A list of members of the household was made giving their ages, occupations, places of work, and particulars of any recent illness. Any known contact between the patient or other member of the household and a previous case was noted, as were visits to or visitors from other places, and the names of previous and subsequent patients in the vicinity. The sources of drinking water, milk, and foodstuffs were entered, and finally the type of house, its sanitary arrangements, and the presence or absence of domestic animals, insects, and vermin. Epidemiological studies were made between April 17 and May 31. They were begun in Savanne and continued in Port Louis and Pamplemousses. Later Black River was surveyed by the V.A.D.s who had assisted us in the other places and given ample proof of their ability. The towns in Plaines Wilhelms were investigated as occasion offered. Altogether 773 cases were studied, but in a few the full questionnaire was not used. In most the data were obtained from the patient or relatives at the house where the illness began, in some they were obtained by questioning the parents when they visited their children in hospital. With the aid of R.A.M.C. orderlies or V.A.D.s as interpreters there was little difficulty in securing answers to the questions asked and the results are probably as reliable as any that can be obtained when investigations are undertaken some weeks after the event. In addition to the 773 cases studied in this way, there were

82 cases for which clinical data were available, a further 163 cases were included which had been notified, mainly from the districts of Rivière du Rempart and Grand Port, but were not seen by us. This total of 1,018 included 41 unnotified cases. It is fewer than the 1,107 notified up to May 31 on account of the rejection of duplicates, untraceable cases, and those in which the diagnosis was doubtful or wrong.

### *Animal Inoculation*

Dr K C Smithburn of the Yellow Fever Research Institute at Entebbe, Uganda, undertook some animal inoculations. Paralytic poliomyelitis resulted in a monkey (*Macacus mulatta*) inoculated with a suspension of the pooled faeces of four family contacts of a case. Two of the contacts were adults and two were children. One of the latter had a febrile illness, which might have been abortive poliomyelitis. Abortive poliomyelitis followed the inoculation of a monkey (*Cercopithecus aethiops johnstoni*) with a suspension of the spinal cord of a fatal case. The virus appeared to be of low virulence for monkeys. Negative results were obtained in 10 other monkeys inoculated with etherized extracts from materials such as flies, faeces, throat swabs, and sewage. The specimens were treated with ether and then kept frozen in a refrigerator in Mauritius and on ice during their 3,000-mile flight to Entebbe. The disappointing inadequacy of this side of the work was due neither to transport difficulties (the Royal Air Force did everything possible to assist us) nor to lack of laboratory facilities, for the Director of the Laboratory at Entebbe, Dr Mahaffy, and Dr Smithburn were willing and able to handle much more material. The trouble was that we arrived late in the course of the epidemic, and had to content ourselves with collecting material from the neighbourhood of the few late cases.

### *Clinical Features*

The clinical findings presented no striking deviation from those usually encountered in epidemics of poliomyelitis. Of the cases considered here 96 per cent were paralysed.

*Site of paralysis* In a sample of 401 cases it was found that the paralysis affected one or both lower limbs in 86 per cent, the lower limbs only being affected in 64 per cent, and lower limbs with other parts of the body in 22 per cent. Upper limbs alone were affected in 10 per cent, and 2 per cent had bulbar paralysis.

*Deaths* There were 58 deaths in cases in which the history of illness given by relatives sustained the diagnosis of poliomyelitis. Of these 58 there were 41 (73 per cent) in which death was due to bulbar or respiratory paralysis, associated with paralysis of the limbs in 26 cases. In the other 17 there were four late deaths due to infection, and 13 severely paralysed cases with no history of respiratory or bulbar paralysis in which the exact mode of death was obscure, the patients having died before we arrived. The case fatality

rate of 6 per cent. calculated from these deaths and the total of 1,018 cases is therefore only an approximation

*Abortive cases* The data concerning abortive cases are unsatisfactory since they had to be based on a history of illness in other members of a household

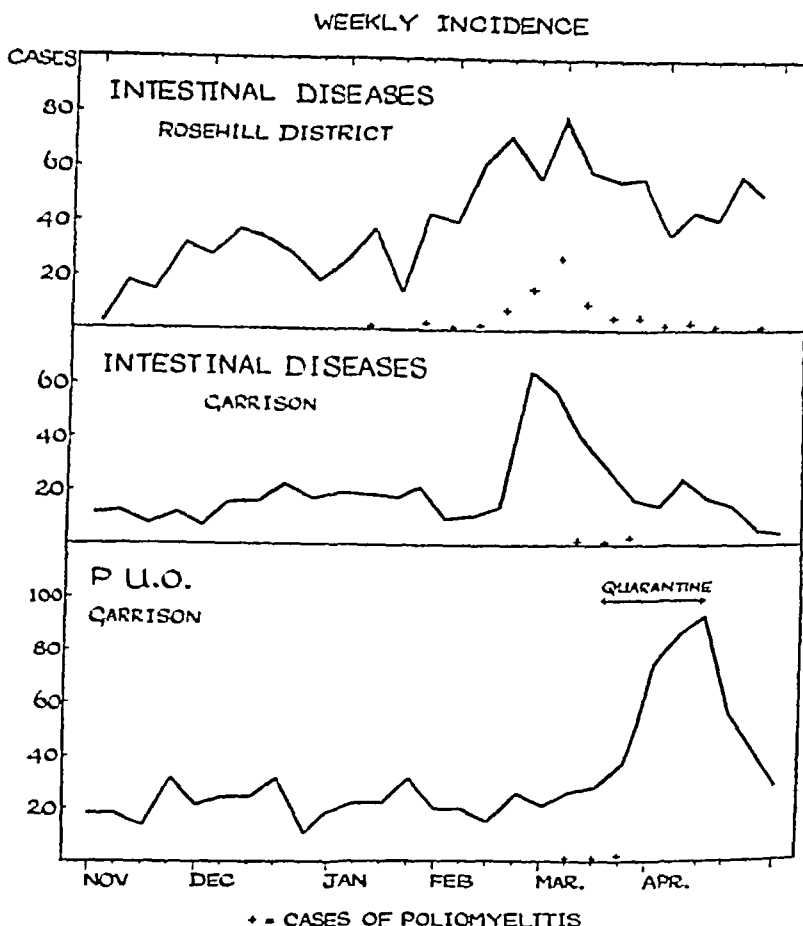


FIG 2 Weekly incidence of diarrhoeas and of pyrexia of unknown origin in the Garrison

occurring at about the time of illness of the frank case, and the inquiry was usually not made until some weeks after the event. After discarding many such cases in which there was a suspicion of malaria, there remained 44 possible instances of abortive poliomyelitis in 773 households. This figure is almost certainly too low. In the garrison, where there were four cases of poliomyelitis, there were in the next six weeks some 200 cases of pyrexia of unknown origin in excess of the average number for the preceding weeks (Fig 2). Malaria was excluded in these cases. Details were available about some of the more severe cases which were sent to hospital, and it seemed that they might have been abortive cases of poliomyelitis. Unfortunately

lumbar punctures were not performed. Others may have been of the same nature or perhaps instances of the 'illness of infection' which is discussed below under 'multiple cases in families'.

The rather explosive curve of this outbreak of fevers, occurring immediately after the cases of poliomyelitis and at a time when the garrison was isolated from the civilians as a precautionary measure, suggested that the virus of poliomyelitis was widely diffused in the garrison and giving rise to fever without paralysis. The diffusion may have been even wider than these figures indicate since men may have been infected and infectious without developing fever.

### *General Epidemiological Findings*

*Prevalence of respiratory and intestinal infections* Weekly returns of sickness in the garrison showed that the incidence of respiratory infections remained fairly constant between November 1944 and April 1945. The curve for intestinal infections showed (Fig 2) an explosive rise in the second half of February which was due to cases arising in many units stationed all over the island. The prevalence of respiratory and intestinal infections in civilians was studied by obtaining from Dr E. H. Madge of the Victoria Hospital, which serves the Rosehill district, the numbers of cases admitted and new out-patients diagnosed each week as suffering from such infections. Respiratory infections fell from a maximum of 60 cases a week in November 1944 to a fairly steady 40 cases a week from January to April 1945. Intestinal infections rose gradually from 20 cases a week in November to 80 cases in the first week of March (Fig 2). The steepest part of the rise was in the first three weeks of February when the poliomyelitis epidemic began in the district. This rise may have been merely a seasonal one, but it showed that there was an increasing prevalence of intestinal infections at the time when the poliomyelitis epidemic began.

*Incubation period* Estimates of the incubation period of poliomyelitis in Mauritius were made from seven cases with short and only possible exposures and from six cases with longer but limited exposures (Fig 3). It was found to be eight to 14 days as is usual in poliomyelitis (Aycock and Kessel, 1943). We have recently obtained detailed information about a merchant seaman of 19 years, who left Mauritius on February 27, landed at Colombo on March 10, and developed poliomyelitis on the 11th. During the two weeks before his departure from Mauritius, he lived aboard his ship in the harbour at Port Louis and went ashore in the evenings, visiting cinemas and taverns. The minimal incubation period in this case was 11 days.

*Multiple cases in families* Multiple cases in families were as usual uncommon, there being only 24 in 1,018 cases. Six of them occurred from eight to 10 days after the first case (Fig 3) and were probably true secondary cases infected by the first case at about the time of its onset. There was one late secondary case on the seventeenth day. The other 17 occurred within five days of the onset of the first case. Four of these 17 cases were in infants.

or very young children, and followed the illness of an older child who had been exposed to infection at school or in the village. It seemed that the older child had introduced the infection into the household and infected the younger child early in the incubation period. Although in the other cases

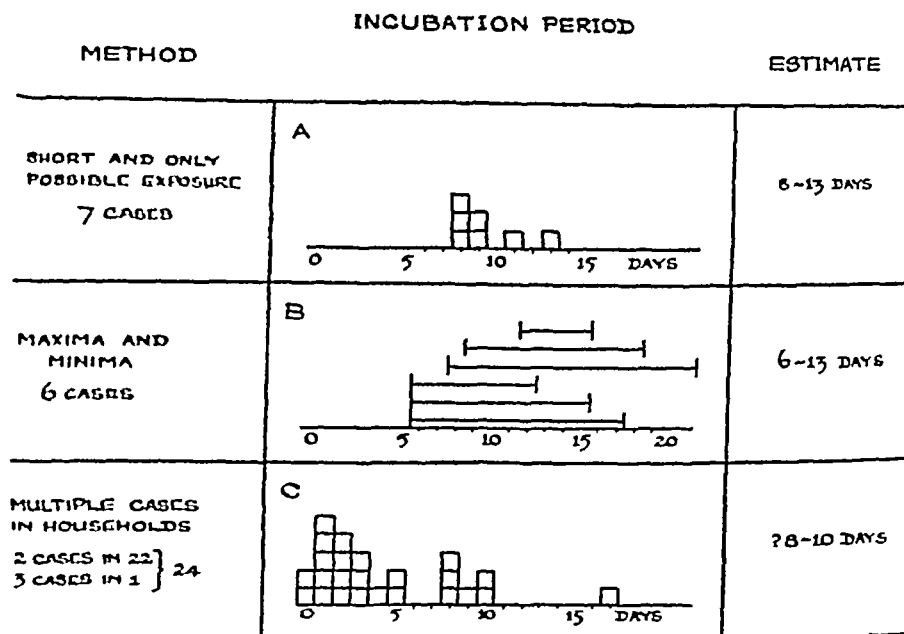


FIG. 3 In A and C, Day 0 is the day of onset of the first case, and each square shows the day of onset of a later case.

In B, Day 0 corresponds to the day of infection and each line shows the limits of the incubation period in a case.

a parallel infection from the same source was possible, the true course of events might have been that the first case infected the second early in the incubation period. Such an explanation would help to account for the observation (Lavinder, Freeman, and Frost, 1918) that 80 per cent of secondary cases of poliomyelitis occur within six days of the first case. The idea that cases may be infectious early in the incubation period is supported by the 'dromedary' type of temperature curve noted in some cases of poliomyelitis in Mauritius and elsewhere. A fever with vague symptoms lasts for a day or two, then after four to seven days of apparent recovery there is a recurrence of fever and paralysis supervenes. If the preparalytic fever is taken as the onset and an incubation period of 10 days is assumed, the first rise of temperature is found to occur between one and four days after infection. It might therefore correspond to an illness of infection. Such an illness of infection, if not followed by further symptoms or signs of poliomyelitis, would constitute the 'minor illness' of Paul and Trask (1932). These authors isolated the virus of poliomyelitis by monkey inoculation of oral washings from two such cases, and pointed out that they corresponded

to Wickman's (1913) conception of an abortive case, and also that Draper (1926) had intimated that the first phase of the 'dromedary' form of clinical poliomyelitis might be the only recognizable phase of the disease in from 50 to 80 per cent of all cases

*Age specific attack rates* (Table II and Fig 4) Age specific attack rates were calculated on the figures of the 1944 census, except in the case of

TABLE II  
*Cases and attack rates per 1,000 in age groups*

Age in months		0 to 2		3 to 5		6 to 8		9 to 11					
Cases		1		8		15		24					
A R		0.3		2.0		3.8		6.0					
Age in years	0	1	2	3	4	5	6	7	8	9			
Cases	48	119	123	123	130	119	86	34	17	7			
A R	4.0	14.9	12.3	12.3	13.0	11.9	8.6	3.4	1.7	0.8			
Quinquennia	0 to 4		5 to 9		10 to 14		15 to 19		20 to 24		25 to 29		Total
Cases	543		263		19		8		11		7		1018
A R	10.7		5.4		0.4		0.2		0.3		0.04		2.4

children under 1 year of age, where the number of notified births was used. The attack rate rose during the four quarters of the first year of life, but the rate in children under 1 year (4 per 1,000) was lower than at ages one to 5 years (12 per 1,000). After the age of 5 the rate declined rapidly. A similar age incidence characterized what appears (Editorial, 1945) to be the first recorded epidemic of poliomyelitis in which 'an epidemic fever spread among all the children in the island (St Helena) about three or five years of age'. All the children who had the fever were affected with a want of growth in some part of their body or limbs' (Bell, 1836). An age incidence of the same sort was found in Malta (Seddon, Agius, Bernstein, and Tunbridge, 1945) and in American towns up to 1918 (Burnet, 1940). A different age incidence was present in American towns after 1930 and in the Melbourne epidemic of 1937-8 where there were relatively more cases in the older age groups (Burnet, 1940). Still more different was the age incidence in the 'virgin soil' epidemics in Guam in 1899, Nauru in 1910, and New Guinea in 1929 where children were notably spared and young adults were chiefly affected (International Committee, 1932). In Mauritius 64 per cent of cases were in children under 5 years, and 95 per cent in children under 10 years. The relative immunity of the older age groups suggested that the outbreak was an epidemic of an endemic disease. The age distribution also presented a challenge to the epidemiologist to find how infection reached the family and attacked the younger members who had fewest contacts outside it.

#### *The Course of the Epidemic*

*In the island as a whole* The weekly incidence of cases (Table III and Fig 5) presented a slight rise in February, a marked rise in the first week of



or very young children, and followed the illness of an older child who had been exposed to infection at school or in the village. It seemed that the older child had introduced the infection into the household and infected the younger child early in the incubation period. Although in the other case

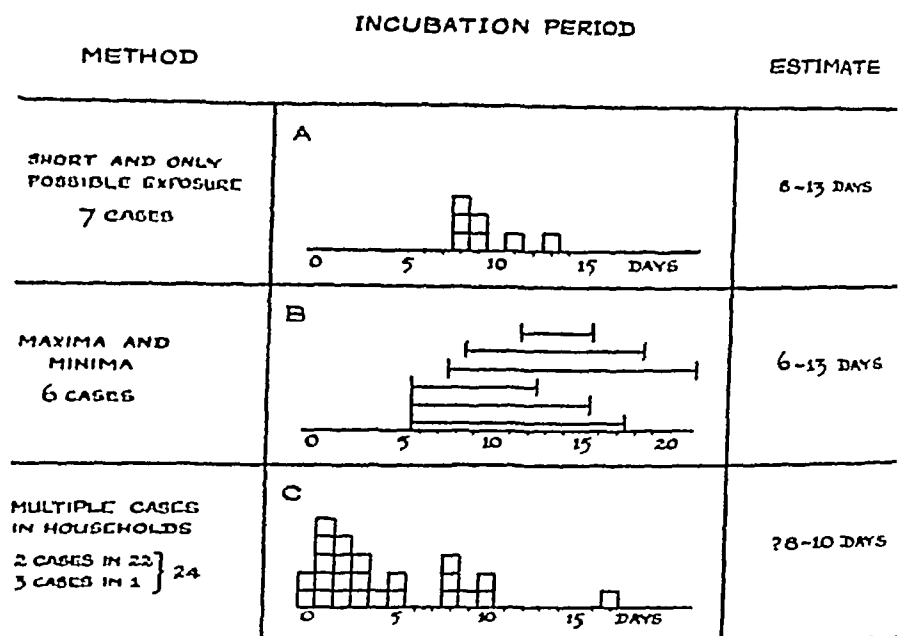


FIG. 3 In A and C, Day 0 is the day of onset of the first case, and each square shows the day of onset of a later case.

In B, Day 0 corresponds to the day of infection and each line shows the limits of the incubation period in a case.

a parallel infection from the same source was possible, the true course of events might have been that the first case infected the second early in the incubation period. Such an explanation would help to account for the observation (Lavinder, Freeman, and Frost, 1918) that 80 per cent of secondary cases of poliomyelitis occur within six days of the first case. The idea that cases may be infectious early in the incubation period is supported by the 'dromedary' type of temperature curve noted in some cases of poliomyelitis in Mauritius and elsewhere. A fever with vague symptoms lasts for a day or two, then after four to seven days of apparent recovery there is a recurrence of fever and paralysis supervenes. If the preparalytic fever is taken as the onset and an incubation period of 10 days is assumed, the first rise of temperature is found to occur between one and four days after infection. It might therefore correspond to an illness of infection. Such an illness of infection, if not followed by further symptoms or signs of poliomyelitis, would constitute the 'minor illness' of Paul and Trask (1932). These authors isolated the virus of poliomyelitis by monkey inoculation of oral washings from two such cases, and pointed out that they corresponded

*In the districts* (Table IV and Fig 6) During January cases occurred in Rosehill, Port Louis, and the Grand Port district No connexion could be found between these cases There was no suggestion of an epidemic till

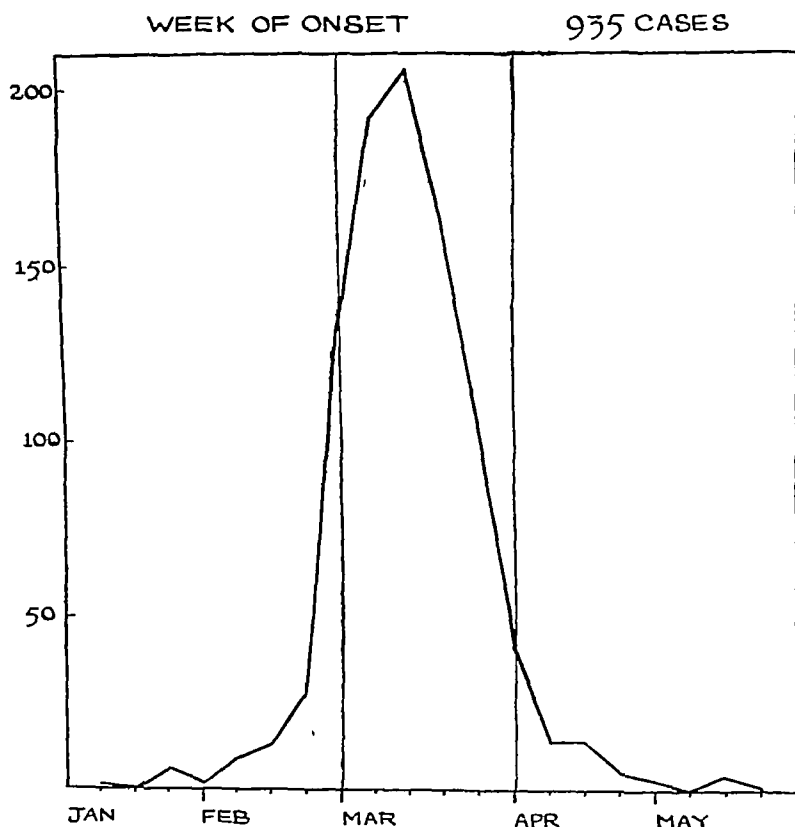


FIG 5 Weekly incidence of cases

TABLE IV

*Cases by weeks and districts in February and March*

	Jan	Week ending							
		Feb				Mar			
		3	10	17	24	3	10	17	24
Rosehill	4	1	2	8	16	27	10	5	5
Port Louis	1	—	3	1	1	14	18	24	11
Grand Port	2	1	3	2	3	12	24	23	24
Rivière du Rempart	—	—	1	—	1	16	29	40	19
Pamplemousses	—	—	—	1	1	36	45	33	32
Savanne	—	—	—	1	1	3	24	21	28
Black River	—	—	—	—	1	1	4	8	5
Flacq	—	—	—	—	2	6	13	14	15
Vacoas	—	—	—	—	1	5	10	11	7
Curepipe	—	—	—	—	—	8	12	18	14
Moka	—	—	—	—	—	4	3	8	2
Total	7	2	9	13	27	132	192	205	162

March, a peak in the third week of March, and a rapid and symmetrical decline. The symmetry suggested contact spread rather than mass infection by food or water. The main wave was very abrupt, covering just six weeks. The Malta epidemic showed a similar curve (Seddon, Agius, Bernstein, and

ATTACK RATES PER 1000 BY AGE

851 CASES

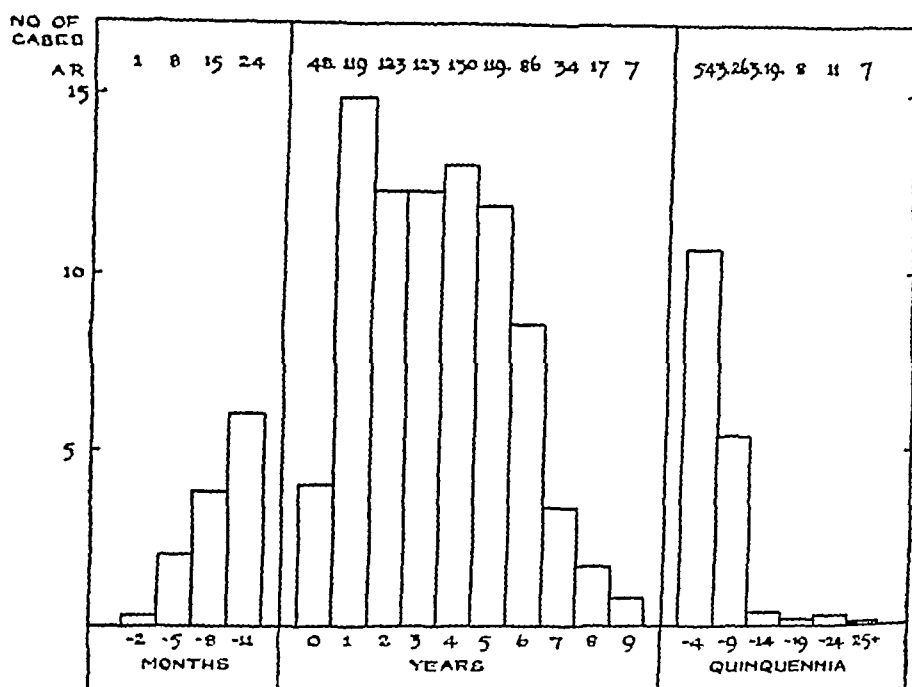


FIG 4 Age attack rates

TABLE III

*935 cases by week of onset*

Month	1	2	3	4	5	Total
Jan	—	1	—	6	—	7
Feb	2	9	13	27	—	51
Mar	132	192	205	162	104	795
Apr	41	14	14	5	—	74
May	3	—	4	1	—	8

Tunbridge, 1945) as did some wards in the Richmond district of New York (Lavinder, Freeman, and Frost, 1918). The somewhat explosive character of the curve resembled that of the curve of deaths in an influenza epidemic, and so suggested a disease with a very short incubation period and a high degree of infectivity affecting a susceptible population. Yet this description certainly did not apply to paralytic poliomyelitis in Mauritius or Malta which was a disease with an incubation period of eight to 14 days, had a low infectivity, and was affecting immunized communities. It might, however, apply to a carrier epidemic of poliomyelitis.

curves was the time required for centrifugal spread of the infection through the district. In Pamplemousses the February cases were in children of vegetable sellers in the Triolet district and the child of a Chinese shopkeeper in another village. The epidemic then spread centrifugally along the roads.

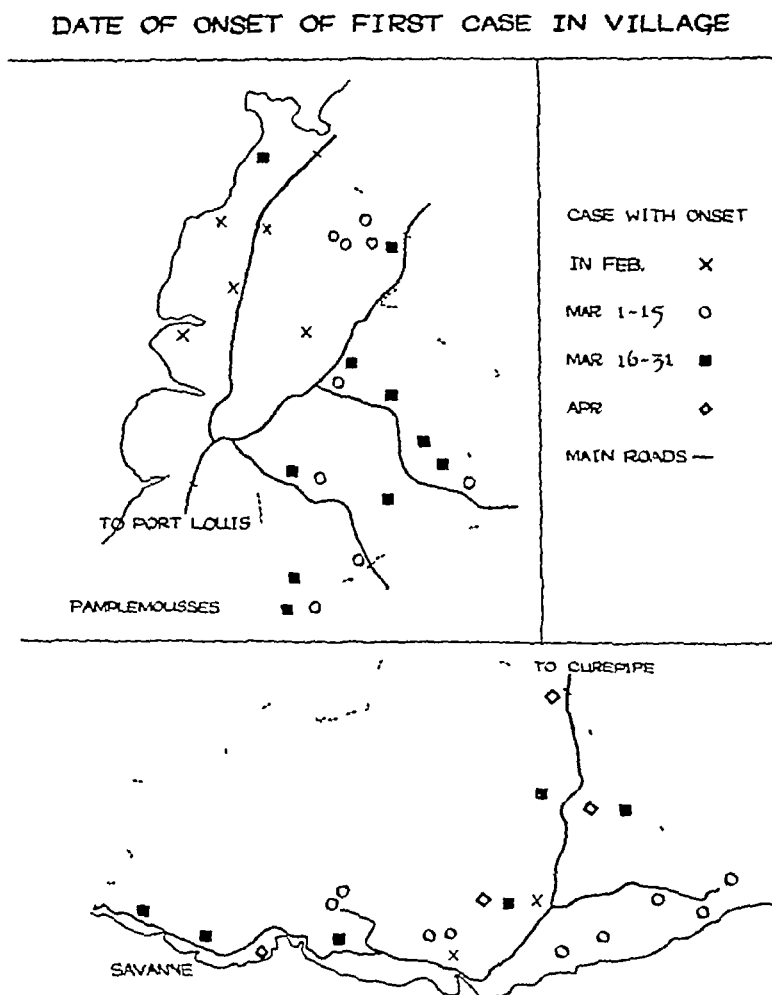


FIG 7 Map of spread in Pamplemousses and Savanne

Some cases in outlying places in the first half of March were apparent exceptions to the centrifugal spread, these patients were children of families with adult males who visited Port Louis frequently. In Savanne there was a spread to the west along the *cul de sac* road during March. In April a few epidemics began in isolated villages and in sugar estates where quarantine regulations had been disobeyed. The first cases in many places were in children of shopkeepers, lorry drivers, and others who had contacts with people in or from other places, in Pamplemousses and Savanne there were 15 instances of the apparent introduction of infection to a family by a healthy

February, when Rosehill (including Beau Bassin and Quatre Bornes) showed a definite rise which reached a peak in the first week of March. During the last two weeks of February one or two cases occurred in other districts, and by the first week of March the epidemic was under way in most districts

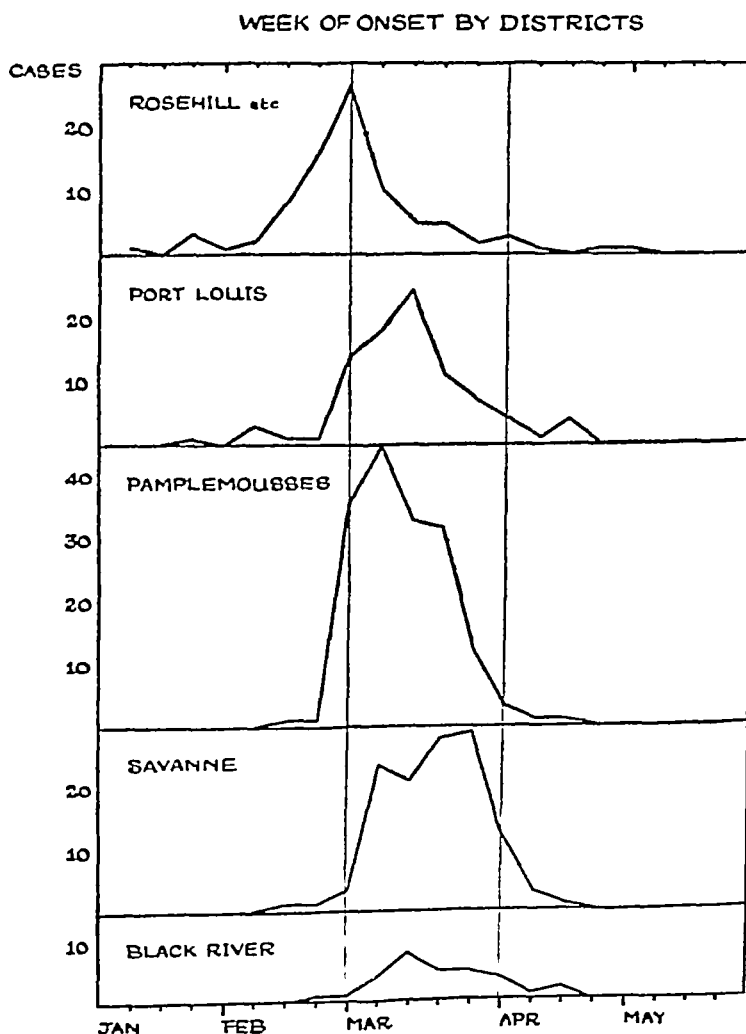


FIG 6 Weekly incidence by districts

The districts in which the epidemic began later had fewer communications with Rosehill and Port Louis. Rosehill and Port Louis showed a rapid decline after their peak, Pamplemousses showed a plateau after the peak, Savanne had a sharp rise in the second week of March and then a plateau rising slowly to a peak in the fourth week of March. Black River had a slow epidemic without a definite peak. Maps of the spread in Pamplemousses and Savanne (Fig 7) showed that the reason for the plateaux in the epidemic

similar curve. The cases were distributed widely over the towns and here again a carrier epidemic was the most probable explanation of the spread of infection. There were a few groups of cases in which transmission by flies was a possibility. However, it was rarely possible to exclude contact between the families in the crowded back-to-back slum dwellings. Indeed, the opportunities for spread by contact were so great that the real problem was not to

TABLE V  
*Enteric fever and poliomyelitis in Triolet*

	Monthly incidence								Total
	1944			1945					
	Oct	Nov	Dec	Jan	Feb	Mar	Apr		
Enteric fever	4	2	10	5	4	2	—	27	
Poliomyelitis	—	—	—	—	6	48	1	55	

	Age distribution					
	0 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29
Enteric fever	3	3	3	12	5	1
Poliomyelitis	45	10	—	—	—	—

	Sex distribution		
	Male	Female	Total
Enteric fever	9	18	27
Poliomyelitis	28	27	55

account for the infection of the patients, but to explain the escape of a large number of other children in very close contact.

The main features of the epidemic in Mauritius as a whole and in the districts, villages, and towns were best explained on the basis of a large-scale carrier epidemic and spread as a rule by contact.

#### *The Method of Spread of Infection*

**Contact.** A history of direct or indirect contact with a previous case within three weeks before the onset of illness was obtained in 13 per cent of 403 cases. The addition of probable cases where contact, though not admitted, had almost certainly occurred brought the total of cases possibly due to direct or indirect contact to 23 per cent. This result is similar to that obtained by Frost (1941). When possible direct and indirect contacts were added—that is visits of the patient or other member of the family to an epidemic area—the total was raised to 50 per cent. The figures for Mauritius might have been higher if field studies had been made at the time the cases occurred, and if it had been possible to include abortive cases, which appeared to be the main agents of spread in Melbourne (Burnet, 1940). Casey (1942) obtained a history of contact, usually for some hours, in 80 per cent of cases in a sparsely populated district of Alabama. The high proportion of possible indirect contacts in the Mauritius cases was a further indication of the

adult male The interval between the first cases in places along the line of spread was often two or three days, so that the rate of spread was faster than would be expected with an eight to 14-day incubation period

*In villages* The daily incidence of cases in Rivière des Anguilles (Fig 8) showed the typical form of the epidemics in villages and sugar estates Cases

### CASES BY DAY OF ONSET

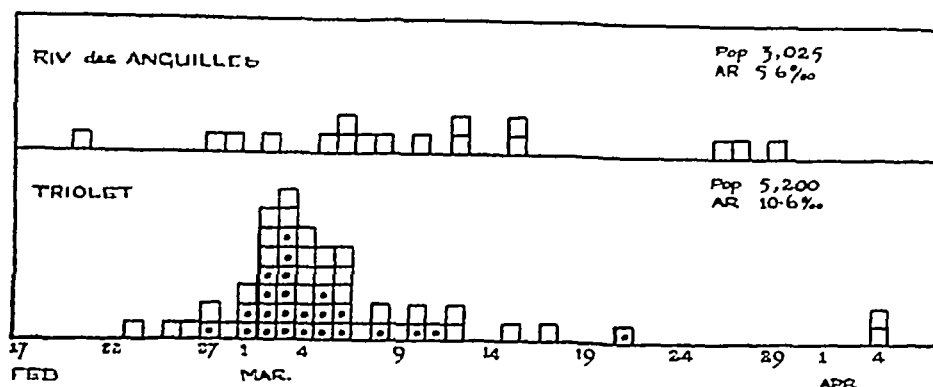


FIG 8 Epidemics in Rivière des Anguilles and Triolet

were spread over two or three weeks with a slight concentration about the middle of the period, but only rarely was there more than one case on one day. The distribution of cases was therefore like that of streptococcal infections and suggested a spread by transient carriers. One notable exception to this epidemic pattern occurred in Triolet in Pamplemousses where the epidemic was explosive (Fig 8). The explosion might have been due to the spread of infection by ices, which consisted of shavings from a block of ice pressed together round a bamboo stick with a dirty rag, and they might have been contaminated by flies or by the hands or by droplets from the nose or mouth of the vendor. One of the early cases in Triolet was the niece of an ice vendor and lived in the same house with him. Half the patients at the peak of the epidemic had eaten ices. In the other cases other methods of spread must have been involved. The sanitary conditions in Triolet were very bad, there was an even greater abundance of flies than elsewhere, and there had been an epidemic of enteric fever in the village. Details of the enteric fever epidemic supplied by the Government Medical Officer showed striking differences (Table V) in the monthly incidence and in the age and sex distribution of cases. Only one person, a girl aged 5 years, contracted both diseases. Many factors were concerned in producing the differences in the epidemiological pattern of the two diseases, but the more rapid diffusion of the poliomyelitis virus would most easily have been accounted for by a widespread carrier epidemic.

*In towns* In Rosehill and Port Louis (Fig 6) there was a fairly rapid rise to a peak and an equally rapid decline. Curepipe (Table IV) showed a

respect of numbers, age distribution, degree of crowding, and experience of cyclone damage, and no difference was found between them and families with a case of poliomyelitis. These similarities gave added significance to the finding that families with a case of poliomyelitis had more outside contacts than the population as a whole.

*Food, water, and milk* Apart from the possible spread of infection by ices in Triolet already described, no evidence was obtained to suggest that infection had been spread by food. Vegetables and fruit were very scarce during February and March on account of cyclone damage. The distribution of water supplies and milk was such as to rule out a spread of infection by them.

*Insect vectors* Flies were prevalent throughout the epidemic, but not conspicuously more so than in previous months. *Musca domestica* was by far the commonest fly, *Stomoxys* was fairly frequent in villages and sugar estates. Apart from small groups of cases, in all of which contact infection was possible, it did not appear that infection could have been transmitted by flies. House flies and *Stomoxys* were collected in the neighbourhood of cases in Savanne and suspensions inoculated into monkeys, but no illness resulted. Spread by anopheline mosquitos was unlikely. *Culex* and *Aedes* were found breeding all over the island in March. *Aedes albopictus* was much commoner than *Aedes aegypti*. However, severe epidemics of poliomyelitis occurred in several villages where the spleen rates were known to be low, and poliomyelitis attack rates were low in other places where spleen rates were high.

*Animals, poultry, and vermin* Inquiries produced no evidence of significant disease in domestic animals, poultry, rats, or mice at the time of the epidemic.

#### *Attack Rates per 1,000 in Certain Sections of the Population*

*Urban and rural attack rates* Attack rates at all ages in the towns of Port Louis and Rosehill (including Quatre Bornes and Beau Bassin) were lower than in the districts of Pamplemousses, Savanne, and Black River (Table VIII). The differences at ages 0 to 4 and 5 to 9 years were 14.9 and 8.0 and were highly significant ( $D/SE = 8.8$  and  $6.7$ ), but at ages over 10 the difference of 0.09 was not significant ( $D/SE = 1.3$ ). Thus the difference between the urban and rural rates was due to lower rates in the towns at all ages. The immunity of town dwellers was apparently acquired early in life. Curepipe showed attack rates intermediate between those in the other towns and those in the districts (Table VIII). The explanation may have been partly that the wealthier inhabitants who had led more sheltered lives were more susceptible. It may also be relevant that the sanitary conditions in the town were most unsatisfactory.

*Attack rates and population density* (Table IX and Fig. 9) Attack rates increased with increasing density of population in the districts of Black River, Savanne, and Pamplemousses where the search for cases was thorough and in a parallel fashion but at a lower level in Moka, Flacq, Grand Port, and



existence of a carrier epidemic preceding the wave of cases of paralysis. Close contact was common between the adult involved as an indirect contact and the patient, in that the adult slept in the same bed as the patient in 10 of the 13 cases classed as definite indirect contact and in 33 of the 93 cases classed as possible indirect. The importance of indirect contact was shown

TABLE VI  
*History of contact in three weeks preceding onset*  
*403 cases*

	Number	Per cent
Direct contact		
Definite	40	9.9
Probable	30	9.7
Possible*	17	4.2
Total	96	23.8
Indirect contact		
Definite	13	3.2
Possible*	93	23.0
Total	106	26.2

\* Visit of patient or member of family to locality where cases of poliomyelitis were occurring

TABLE VII  
*Outside contacts of families*

A Adult males in 'away trades'

	Population		Per cent away trades	
	Total	Poliomyelitis	Total	Poliomyelitis
Pamplemousses	10,332	242	15.0	39.0 ± 1.0
Savanne	12,293	180	4.3	8.3 ± 2.0

B Children attending school

	Children at school		Children at school, percentage of total population of district	
	Total	Poliomyelitis	Total	Poliomyelitis
Pamplemousses	1,938	94	5.7	10.6 ± 1.0
Savanne	1,935	91	5.8	12.6 ± 1.2
Port Louis (town)	8,760	102	15.0	25.0 ± 2.1

in another way. The adult males in the families with a case of poliomyelitis were classified into those working in trades at home or away—sugar-estate workers, gardeners and the like in home trades, and vegetable sellers, commercial travellers, lorry and bus drivers and the like in away trades. The results were compared with the census figures for the occupations of adult males in the district. The percentage of adult males in away trades (Table VII) was significantly higher in families with a case of poliomyelitis than in the population of the district. Similarly there was a significantly higher percentage of children attending school in the families with a case than in the population of the district. Control families were studied in

exposed to infection than the Indian or Creole children on account of the many extrafamilial contacts of the Chinese adults in their own shops and in markets in the towns. The same factor was probably responsible for the high attack rate in the Chinese quarter of Port Louis, which was 2.7 as compared

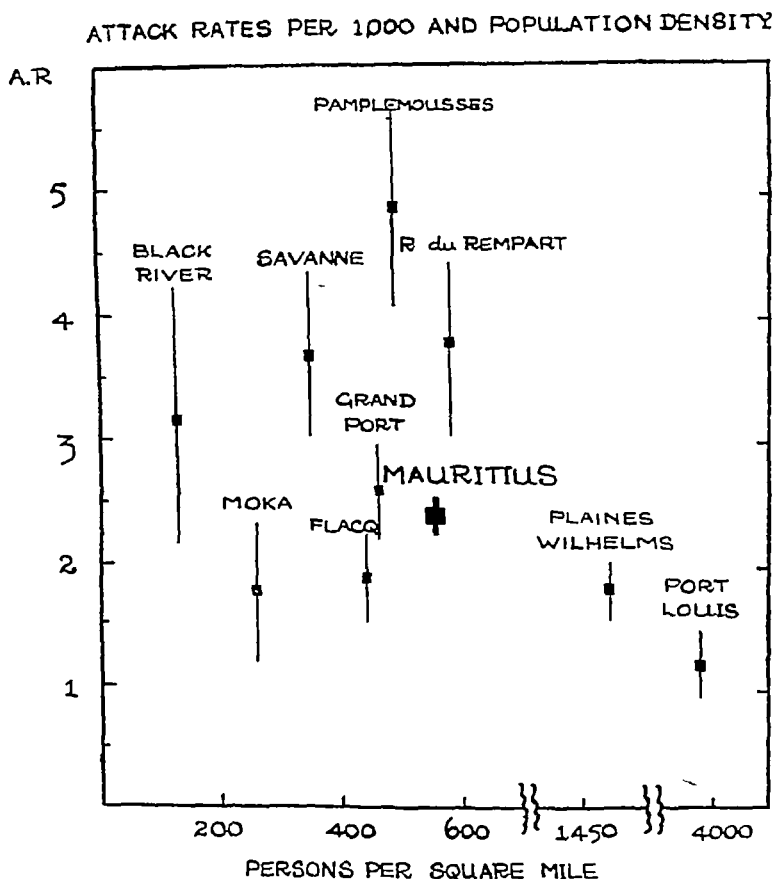


FIG 9 The vertical lines show the extent of a deviation of twice the standard error above and below the estimated attack rate

TABLE X

*Sex specific attack rates per 1,000 on 0 to 9 age group*

	Males	Females
Urban	7.1	3.4
Port Louis	6.5	2.5
Rosehill	8.0	5.3
Rural	18.4	16.2
Pamplemousses	19.7	19.5
Savanne	17.6	13.2
Black River	13.0	14.2

with 1.6 in the next highest of the 12 census blocks into which the town was divided, and with 1.2 for the whole town

Rivière du Rempart where the search was less thorough. This relationship supports the idea that spread by contact was important. The rates in Port Louis and Plaines Wilhelms showed an inverse relationship to population density. Apparently above a certain density the degree of immunity in

TABLE VIII  
*Urban and rural attack rates per 1,000*

	Age group—years				All ages
	0 to 4	5 to 9	10 to 14	over 15	
Urban	8.1	3.2	—	—	1.4
Port Louis	6.7	3.4	—	—	1.2
Rosehill	10.3	2.8	—	—	1.6
Rural	23.0	11.2	0.7	0.1	4.2
Pamplemousses	27.9	10.8	—	—	4.9
Savanne	19.5	11.4	—	0	3.7
Black River	16.2	10.9	—	—	3.2
Curepipe	11.6	7.0	—	0.5	2.5

0 = No cases

— = Less than five cases

TABLE IX  
*Attack rates per 1,000 by districts in relation to population density*

District	Attack rate ± standard error	Persons per sq. mile
Pamplemousses	4.9 ± 0.4	495
Savanne	3.7 ± 0.3	349
Black River	3.2 ± 0.5	125
Plaines Wilhelms	1.8 ± 0.1	1,531
Port Louis	1.2 ± 0.1	3,997
Rivière du Rempart	3.8 ± 0.3	583
Grand Port	2.6 ± 0.2	463
Flacq	1.9 ± 0.2	442
Moka	1.8 ± 0.3	257
Mauritius	2.4 ± 0.1	582

creased and produced a lower attack rate despite the greater opportunities for contact spread.

*Sex specific attack rates* (Table X) Rates were calculated only for the population of males and females under 10 years, since the normal proportion of males to females over that age had been upset by enlistment of men in the armed forces. In rural districts there was a slightly higher rate in males as is usual in poliomyelitis. In towns the difference was greater, due perhaps in part to the greater exposure of the boys to infection and in part to their greater physical exertion which predisposed to the development of paralysis. Observations suggested that the boys differed from the girls in these respects more in the towns than in the country.

*Race specific attack rates* (Table XI) The attack rate was higher in the Chinese than in the other two racial groups for which census figures were available, and particularly high in the 0 to 4 years age group of rural children. The most probable explanation is that these children were more

overcrowding due to air raid damage (though it had passed the peak) and there had been an epidemic of enteric fever in the months before the poliomyelitis epidemic began. In Mauritius it was found that the poliomyelitis patients had not had diarrhoea previously and in Malta that the poliomyelitis patients had not had enteric fever. The intestinal disease did not act by increasing the susceptibility of individuals to poliomyelitis. Since it is known (Ward and Sabin, 1944, Kessel and Moore, 1945) that the poliomyelitis virus can be recovered from faeces in non-epidemic periods, it is perhaps justifiable to suggest that the intestinal disease acted by facilitating the passage of the virus and that the virus then 'got its teeth', to adapt a phrase used by Andrewes (1940), that is, became more invasive and more pathogenic. In Mauritius this change appeared to occur only in the Rosehill district, but in Malta the simultaneous appearance of multiple foci suggested that the change occurred in several places at the same time.

*The method of spread of infection.* In Mauritius contact appeared to be the most important factor in the spread of infection, using the term to include all the possible combinations of case to carrier transfer and leaving for later discussion the question of the relative importance of the pharynx and faeces as a source of virus. There were instances where healthy adults appeared to act as carriers. The pattern of spread in villages suggested a spread by transient carriers. The rate of spread from village to village and the explosive nature of the main curve of the whole epidemic suggested a shorter period between exposure and the development of infectivity than the eight- to 14-day incubation period found in paralytic cases. The 'dromedary' temperature curve in some cases was evidence of an illness occurring between one and four days after effective exposure to infection. Taken together these ideas led to the suggestion that the commonest result of infection with the poliomyelitis virus was the development, one to four days later, of infectivity with, or more usually without, symptoms. Only a small proportion of the persons so infected developed paralysis eight to 14 days after infection. On this hypothesis the spread of infection was due mainly to carriers who became infectious for a short time a few days after exposure. This resulted in a large carrier wave of the influenza type, followed about a week later by the wave of cases of paralysis, a much smaller wave but of the same explosive, influenza-like type.

*The relative importance of the pharynx and the intestine as a source of infection.* The virus of poliomyelitis has been recovered from the pharynx of 50 per cent of patients during the first week of illness (Howe, Wenner, Bodian, and Maxcy, 1944) and from the pharynx of a patient five days before symptoms developed (Taylor and Amoss, 1917). It has been isolated from the faeces of patients 19 and 11 days before the onset of symptoms (Brown, Francis, and Pearson, 1945, Pearson and Rendtorff, 1945) and for weeks or even months thereafter (Lépine, Sédallian, and Sautter, 1939, Horstmann, Ward, and Melnick, 1944). The virus has also been isolated from the nasopharynx of adult contacts (Flexner, Clark, and Fraser, 1913) and from the

*Secondary attack rates in families* (Table XII) Persons in the same family as a poliomyelitis patient had a higher attack rate than the general population. Whether the later cases are considered as parallel primary cases or true secondary cases, the higher rates were evidence of the importance of contact in the spread of infection.

The differences in attack rates on several sections of the population are therefore explicable in terms of an immunity in town dwellers leading to

TABLE XI  
*Race and age specific attack rates per 1,000*

Population	Age group—years				All ages
	0 to 4	5 to 9	10 to 14	over 15	
General					
Urban	6.7	2.6	—	—	1.1
Rural	17.1	12.2	0	—	3.5
Indian					
Urban	9.6	2.9	0	—	1.6
Rural	24.4	10.4	0.0	—	4.2
Chinese					
Urban	7.8	7.9	0	—	2.6
Rural	35.0	—	0	0	9.9

0 = No cases

— = Less than five cases

TABLE XII  
*'Secondary' attack rates in 452 families*

	Age group—years				All ages
	0 to 4	5 to 9	10 to 14	over 15	
Exposed	319	384	224	1,192	2,119
Attacked	14	5	0	1	20
A R per 1,000	44.0	13.1	0.0	—	9.4
A R per 1,000 whole population	10.7	5.4	0.4	0.5	2.4

low rates and an increased risk of exposure leading to high rates. This finding strengthens the conclusion already drawn from field studies that contact was an important factor in the spread of infection.

### Discussion

*The origin of the epidemic* Inquiries about the few persons who arrived in Mauritius between October 1944 and April 1945 failed to produce any evidence that infection could have been introduced from South Africa where an epidemic of poliomyelitis was in progress at the time. The age incidence in Mauritius suggested that the outbreak was an epidemic of an endemic disease. The epidemic was at first confined to the Rosehill district. It began immediately after the second cyclone when there was more overcrowding than usual and when the prevalence of intestinal diseases was increasing. In Malta likewise there was at the time of the poliomyelitis epidemic great

overcrowding due to air raid damage (though it had passed the peak) and there had been an epidemic of enteric fever in the months before the poliomyelitis epidemic began. In Mauritius it was found that the poliomyelitis patients had not had diarrhoea previously and in Malta that the poliomyelitis patients had not had enteric fever. The intestinal disease did not act by increasing the susceptibility of individuals to poliomyelitis. Since it is known (Ward and Sabin, 1944, Kessel and Moore, 1945) that the poliomyelitis virus can be recovered from faeces in non-epidemic periods, it is perhaps justifiable to suggest that the intestinal disease acted by facilitating the passage of the virus and that the virus then 'got its teeth', to adapt a phrase used by Andrewes (1940), that is, became more invasive and more pathogenic. In Mauritius this change appeared to occur only in the Rosehill district, but in Malta the simultaneous appearance of multiple foci suggested that the change occurred in several places at the same time.

*The method of spread of infection.* In Mauritius contact appeared to be the most important factor in the spread of infection, using the term to include all the possible combinations of case to carrier transfer and leaving for later discussion the question of the relative importance of the pharynx and faeces as a source of virus. There were instances where healthy adults appeared to act as carriers. The pattern of spread in villages suggested a spread by transient carriers. The rate of spread from village to village and the explosive nature of the main curve of the whole epidemic suggested a shorter period between exposure and the development of infectivity than the eight- to 14-day incubation period found in paralytic cases. The 'dromedary' temperature curve in some cases was evidence of an illness occurring between one and four days after effective exposure to infection. Taken together these ideas led to the suggestion that the commonest result of infection with the poliomyelitis virus was the development, one to four days later, of infectivity with, or more usually without, symptoms. Only a small proportion of the persons so infected developed paralysis eight to 14 days after infection. On this hypothesis the spread of infection was due mainly to carriers who became infectious for a short time a few days after exposure. This resulted in a large carrier wave of the influenza type, followed about a week later by the wave of cases of paralysis, a much smaller wave but of the same explosive, influenza-like type.

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faeces of contacts (Francis, Krill, Toomey, and Mack, 1942, Pearson, Brown, Rendtorff, Ridenour, and Francis, 1945) The problem is to decide which is the more important source of virus for the transmission of infection Several points suggest that the pharynx is important

1 The infectious period of the disease determined epidemiologically corresponds to the period when the virus is found in the pharynx (Aycock and Kessel, 1943)

2 In Mauritius and in other places before 1930 (Burnet, 1940) adult carriers appeared to play an important part in the spread of infection, whereas it has been less easy to demonstrate the virus in the stools of adults than in children under eight years of age (Paul, Havens, and van Rooyen, 1944)

3 In Mauritius casual contact as between children in a doctor's waiting room or between adults buying and selling in the market apparently sufficed to transmit infection

4 The distribution of cases in towns and villages and over the island was of the diffuse sort found in diseases where infection is spread from the mouth or nose

Studies of the distribution of faecal excreters in the neighbourhood of cases (Francis, Krill, Toomey, and Mack, 1942) or during an epidemic (Pearson, Brown, Rendtorff, Ridenour, and Francis, 1945) have shown that they are more frequent among intimate contacts than among casual contacts of cases, and still less frequent in the general population This distribution of the virus in faeces is of the sort expected in a disease spread by faecal contamination, where cases and carriers are concentrated somewhat irregularly among the intimate contacts of known cases The distribution of cases of paralytic poliomyelitis in Mauritius was much more diffuse, so that although the poor sanitary conditions offered many opportunities for spread from faeces it seemed necessary to postulate a spread of infection from the pharynx of cases and carriers for a short time some few days after exposure This does not mean that spread of poliomyelitis virus from faeces does not occur, evidence suggesting that it does so is contained in several of the papers just cited and in one by McAlpine (1945) It appeared, however, in Mauritius that spread from faeces was not the only means of spread nor perhaps the most important one Therefore in attempting to control the spread of poliomyelitis it would be wise to employ not only methods similar to those used to prevent the spread of bacillary dysentery, but also methods designed to prevent the spread of a respiratory infection such as meningo coccal meningitis

#### *Summary*

1 An epidemic of poliomyelitis occurred in Mauritius in February, March, and April 1945 There were at least 1,018 cases and the attack rate was 2.4 per 1,000 of population The case mortality was about 6 per cent

2 The incubation period was the usual eight to 14 days There were only 23 families with more than one case The attack rate in the first year of

life was low, at ages one to five years it was about 12 per 1,000, from six to nine years it declined rapidly, and remained low at older ages

3 The epidemic began in one urban district and spread rapidly all over the island. The curve of the epidemic had a symmetrical and somewhat explosive character. A centrifugal spread was observed along the roads of two rural districts and healthy adult males appeared to act as carriers of the infection.

4 The results of field studies and comparisons of attack rates in various sections of the population indicated that the chief factor in the spread of infection was human contact.

5 The epidemic began soon after a cyclone had caused much damage all over the island and at a time when intestinal diseases were increasing in prevalence. It is suggested that the endemic poliomyelitis virus underwent a modification and became more pathogenic and more invasive.

6 The rapidity of the spread of infection and the character of epidemic curves for the whole epidemic and for individual towns and villages suggested a spread by transient carriers who became infectious a few days after exposure. A widespread carrier epidemic apparently spread rapidly among adults and children and was followed about a week later by a much smaller epidemic of cases of poliomyelitis.

7. It was probable that the presence of the virus in the pharynx of patients and carriers was at least as important for the spread of infection as was its presence in faeces.

This paper is based on a report made by us to the Secretary of State for the Colonies. One of us (A. M. McF.) was seconded to the investigation from the Emergency Public Health Laboratory Service (directed by the Medical Research Council) and received a grant from the Colonial Office. Another (G. W. A. D.) was seconded from the Medical Services, East Africa Command. For these arrangements we wish to thank Sir Edward Mellanby and Brigadier H. S. Cormack respectively. It is a pleasure to record our indebtedness to the many people in Mauritius who helped in this work, in particular to the Government Medical Officer for Pamplemousses and the Sanitary Inspectors in Savanne, also to the Director of the Medical and Health Department, the Registrar General, the Census Officer, and the Director of the Royal Albert Observatory who provided us with statistics. The Officer Commanding Troops and Station Medical Officer, Mauritius, generously supplied us with competent clerks and interpreters and placed an Army car at our disposal. We were also helped by the Quartermaster of the Station Hospital and the Officers Commanding the Malaria and Field Hygiene Sections. Perhaps our greatest debt is to the V. A. D.s without whose intimate knowledge of the island and its peoples the detailed fieldwork would have been impossible.



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## APPENDIX

## Anterior Poliomyelitis

Case No .....

Date ..... 1945

## CASE SHEET

Date of onset  
 Date notified  
 Hospital admission  
 Names  
 Race  
 Residence at onset  
 Previous residence  
 Occupation

Doctor  
 G M O  
 Discharge  
 Sex      Date of birth  
 Religion  
 Date of change  
 Place

C.N.S		Date of onset	SYMPTOMS	
				Duration
Irritability				
Somnolence				
Headache				
Eye signs				
Dysphagia				
Dyspnoea				
Tachypnoea				
Rigidity Neck				
Spine				
Paralysis				
ALIMENTARY				
Anorexia				
Vomiting				
Abdominal pain				
Bowels				
RESPIRATORY				
Sore throat				
Cough				
Bronchitis				
URINARY				
JOINTS				
FEVER				
		PREVIOUS ILLNESS		
Injury				
Injections				
Vaccination				
Diarrhoea				
Scabies				
Other conditions				
		HOUSEHOLD		
Age and sex		Status	Occupation	Place
M      F				
1				Recent illness
2				
3				
4				
5				
6				
7				
8				
No in room with case		No in bed with case		

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# THE OCULAR MANIFESTATIONS OF TUBEROSE SCLEROSIS<sup>1</sup>

By G S HALL

(From the Birmingham United Hospital)

With Plates 16 to 20

## Introduction

WITHIN recent years an increasing literature has reflected the interest which tuberose sclerosis continues to receive, and it is now established that neither adenoma sebaceum, fits, nor mental deficiency are essential features of the disorder. Of particular interest and importance to the physician and ophthalmic surgeon are the ocular manifestations which occur, for it is sometimes on the presence of these alone that the recognition of *formes frustes* depends. Best known of these ocular manifestations are the retinal nodules (later named phakomata), and since van der Hoeve first described them in 1920 accounts of their ophthalmoscopic appearance have continued to be recorded. Nevertheless, personal experience has shown that these lesions are still not as widely known as their importance demands, and this view receives some support from the smallness of the English literature concerning them (van der Hoeve, 1920, 1923b, 1932, 1940, Critchley and Earl, 1932, Brain and Greenfield, 1937, Wilson, 1940, Duke-Elder, 1940, Hall, 1940, Martin and Savin, 1941). It is difficult to assess their frequency, but Wilson's (1940) statement that by comparison with the skin lesions the retinal ones are much more rare is probably correct. Van der Hoeve (1920) found them in both fundi of six patients suffering from the disorder, and the present writer has observed them in six (bilateral in three) out of 20 patients. It is to be remembered that a satisfactory ophthalmoscopic examination may be impossible in this condition without the aid of a general anaesthetic, and the lesions may well occur more frequently than is realized.

Clinically there are two types of retinal nodules and these occasionally coexist. The more frequent type is the generally small but occasionally quite large, oval or circular, greyish-white, grey-green, white, or faintly yellow nodule, flat or slightly raised from the surface, single or multiple, and occurring in any part of the retina. There is also the large nodular type which has a predilection for the region of the optic disk, projects forwards into the vitreous, and is not infrequently cystic. Van der Hoeve (1921) observed with the ophthalmoscope cystic degeneration of such a lesion

<sup>1</sup> Received January 25, 1946

## CONTACT WITH CASES

Direct with case name	No	date	19
Public places visited			
Absences from home	date	place	
Cases in place visited			
Indirect contact			
Nearest previous case			
Nearest subsequent case			

---

## FOOD, ETC

Water from	solely, principally	occasionally			
„ boiled	chlorinated				
Milk beverage	on cereals	in coffee			
„ boiled	Pasteurized	source			
Elsewhere than at Home	....	.. ..			
Meals	Meat *	Fish *	Fruit *	Vegetables *	Other *
A M					
MIDDAY					
P M					
SOURCE					

\* (State whether raw or cooked )

---

## ENVIRONMENT

Type of house	Roof	Walls	Floor	
Cyclone damage	January	February	April	
Number of rooms	Light	Space	Ventilation	
Sewage disposal		Garbage disposal		
Yard		Condition		
General sanitary conditions				
Distance from nearest stable		byre	hen run	
Animals on premises	Horses	Cows	Pigs	Goats
	Sheep	Dogs	Cats	Poultry
	Rats	Mice		
Sickness of animals				
Insects prevalent	Flies	Mosquitoes	Aedes	Fleas
	Cockroaches	Bed bugs	Ticks	Lice

one-third of the cases of drusen of neurological abnormalities consistent with those encountered in tuberose sclerosis, and the congenital heredo-familial tendencies of both conditions and their association with renal disorders and congenital anomalies

Pigmentary changes in the retina may be present (Horniker and Salom, 1932, Salom, 1932) consisting of yellowish-red or blurred pigmented spots, clearly demarcated naevoid spots and naevi, and changes resembling, if not identical with, those of retinitis pigmentosa. In only one personally observed case were gross pigmentary changes present. The patient, a man aged 43 years, had well-marked symptoms and signs of the disorder. In the left eye there were extensive pigmentary changes overlying an ill-defined mass of whitish lesions adjacent to the upper part of the disk, while in the temporal periphery of the retina there were several quite large whitish cystic lesions, some nodular and all of them intimately associated with profound pigmentary changes (Plate 16, Fig 1)

Papilloedema, probably always secondary to intracranial hypertension resulting from a paraventricular glomatous tumour, has been recorded by Schuster (1914), Critchley and Earl (1932), Guillain and Lagrange (1934), Walsh, Koch, and Brunsting (1938), Koch and Walsh (1939), Hall (1940), Moolten (1942), and Krug (1944)

Pallor of the optic disks sometimes occurs (van der Hoeve, 1921), either from consecutive atrophy following papilloedema (Seidel, 1938, Koch and Walsh, 1939, Hall, 1940) or from a tumour nodule developing at the nerve head (Ross and Dickerson, 1943), occasionally the pale and waxy appearance of the disk resembles colloid degeneration (Sachs and Shaskan, 1944)

Cataract may be a feature. Yakovlev and Guthrie (1931), Stewart and Bauer (1932), and Ford (1937) all refer to its occurrence in tuberose sclerosis, but an extensive search of the literature has failed to find any case record describing its presence, though a case recorded by Horniker and Salom (1932) developed a cataract after attempted X-ray treatment of adenoma sebaceum. Ross and Dickerson (1943) gave details of a patient with a posterior polar cataract in one eye, but made no further reference to it in their histological report. Grinker (1932) stated that deposits of growth had been found in the lens, a finding confirmed by Hall (1940) who has described the presence in the upper part of a lens of a lobulated opacity which histological examination proved to be a small centrally placed nodule of growth.

Conjunctival lesions occur (Luo, 1940) consisting of small, greyish-white, slightly elevated, and pedunculated nodules, symmetrically placed on the conjunctivae of the lower lids. Histologically there is proliferation of collagenous fibrous tissue with an absence of elastic fibres. Luo regarded the lesions as analogous to the fibromata of the skin and the fibromatous proliferations which sometimes exist on the buccal mucosa and the hard palate in this disorder.

Phthisis bulbi may develop (Luo, 1940), the cornea becoming opaque, flat, and almost entirely replaced by scar tissue, the sclera thickened and

with local haemorrhage therefrom and rupture into the vitreous, apparently resulting in the development of further lesions elsewhere in the retina—'a veritable picture of intra-ocular metastasis' (van der Hoeve, 1932). These lesions appear to be relatively avascular and usually are not associated with any alteration in the neighbouring blood-vessels. Occasionally, however, vascular changes are present. Thus van der Hoeve (1920, 1921) recorded nodules in association with multiple aneurysms of a retinal artery, Gottheb and Lavine (1925) numerous capillaries interwoven into a fine mesh which dipped into the tumour substance, Horniker and Salom (1932) haemorrhages (retinal and vitreous) with perivascular changes, and Hall (1940) an aneurysmal swelling on an artery adjacent to a nodule, and in another case, perivascular changes with an associated vascular naevoid appearance, similar perivascular changes have also been described by Bau-Prussakowa (1933), Martin and Savin (1941), and Ross and Dickerson (1943). Loewenstein and Steel (1941) described an ophthalmoscopic appearance of exudative retinitis, retinitis proliferans with new vessel formation, and angiomatous retinal nodules in association with a diffuse, grey-green, subretinal mass, whilst in the enucleated eye of their patient, retinal detachment and disintegration, little knob-shaped retinal tumours, angiomatous retinal masses composed of thin walled vessels, an angioma of the choroid, and a pyramidal tumour of the disk were observed. An appearance resembling retinitis proliferans was also noted by Bau-Prussakowa (1933), whilst the occurrence of choroiditis (Schuster, 1914), retinal colobomas (Rintelen, 1936), chorio-retinitis, a marked increase of retinal pigment unaccompanied by any other ocular changes, and retinoconus (Ross and Dickerson, 1943) are also on record.

Reese (1940) has drawn attention to the similarity between the ophthalmoscopic appearance of the large, glittering, white, mulberry-like nodule growing from the optic disk in tuberose sclerosis and that seen in the condition known as drusen or hyaline bodies of the optic nerve. He points out that though drusen occur mostly in otherwise healthy people, in quite a number of instances they are associated with some neurological abnormality, the commonest being visual field changes unexplainable on the basis of the drusen, optic atrophy out of proportion to the lesion of the nerve, convulsions, psychoses, disturbance of gait and speech, hydrocephalus, and papilloedema. Of further interest is the occasional association of drusen with renal involvement ('kidney trouble', 'Bright's disease', 'uraemia'), cardiac lesions (twice reported), and various congenital anomalies of the eye, such as cataract, retinal coloboma, subluxation of the lens, an abnormal retinal vein, a persistent hyaloid artery, and retinitis pigmentosa. Reese (1940) concluded, therefore, that drusen of the optic nerve are a feature of tuberose sclerosis, and that they may appear as part of the fully developed disease, but more frequently are seen in its incomplete forms. He based his opinion on the similarity of the pathological process in the two conditions, the occurrence in tuberose sclerosis of lesions in the optic nerve having the identical clinical appearance of so-called drusen of the optic nerve, the occurrence in

one-third of the cases of drusen of neurological abnormalities consistent with those encountered in tuberose sclerosis, and the congenital heredo-familial tendencies of both conditions and their association with renal disorders and congenital anomalies

Pigmentary changes in the retina may be present (Horniker and Salom, 1932, Salom, 1932) consisting of yellowish-red or blurred pigmented spots, clearly demarcated naevoid spots and naevi, and changes resembling, if not identical with, those of retinitis pigmentosa. In only one personally observed case were gross pigmentary changes present. The patient, a man aged 43 years, had well-marked symptoms and signs of the disorder. In the left eye there were extensive pigmentary changes overlying an ill-defined mass of whitish lesions adjacent to the upper part of the disk, while in the temporal periphery of the retina there were several quite large whitish cystic lesions, some nodular and all of them intimately associated with profound pigmentary changes (Plate 16, Fig 1)

Papilloedema, probably always secondary to intracranial hypertension resulting from a paraventricular glomatous tumour, has been recorded by Schuster (1914), Critchley and Earl (1932), Guillain and Lagrange (1934), Walsh, Koch, and Brunsting (1938), Koch and Walsh (1939), Hall (1940), Moolten (1942), and Krug (1944)

Pallor of the optic disks sometimes occurs (van der Hoeve, 1921), either from consecutive atrophy following papilloedema (Seidel, 1938, Koch and Walsh, 1939, Hall, 1940) or from a tumour nodule developing at the nerve head (Ross and Dickerson, 1943), occasionally the pale and waxy appearance of the disk resembles colloid degeneration (Sachs and Shaskan, 1944)

Cataract may be a feature. Yakovlev and Guthrie (1931), Stewart and Bauer (1932), and Ford (1937) all refer to its occurrence in tuberose sclerosis, but an extensive search of the literature has failed to find any case record describing its presence, though a case recorded by Horniker and Salom (1932) developed a cataract after attempted X-ray treatment of adenoma sebaceum. Ross and Dickerson (1943) gave details of a patient with a posterior polar cataract in one eye, but made no further reference to it in their histological report. Grinker (1932) stated that deposits of growth had been found in the lens, a finding confirmed by Hall (1940) who has described the presence in the upper part of a lens of a lobulated opacity which histological examination proved to be a small centrally placed nodule of growth.

Conjunctival lesions occur (Luo, 1940) consisting of small, greyish-white, slightly elevated, and pedunculated nodules, symmetrically placed on the conjunctivae of the lower lids. Histologically there is proliferation of collagenous fibrous tissue with an absence of elastic fibres. Luo regarded the lesions as analogous to the fibromata of the skin and the fibromatous proliferations which sometimes exist on the buccal mucosa and the hard palate in this disorder.

Phthisis bulbi may develop (Luo, 1940), the cornea becoming opaque, flat, and almost entirely replaced by scar tissue, the sclera thickened and



TABLE I

*Summarizing main histological features recorded in examinations of retinal and disk lesions*

Author	Site of tumour	Retinal layers involved	Type of tissue	Special features
van der Hoeve (1923a)	Optic disk	Nerve fibre and ganglion cell layers	Nerve fibres and undifferentiated embryonic cells—'glioneurocytes'	Cystic degeneration, haemorrhage and rupture into vitreous, intra ocular metastasis
van der Hoeve (1932)	Retina	Nerve fibre layer	—	—
Schob (1925)	Retina	Nerve fibre layer	Glial	—
Fierz (1930)	Retina	Nerve fibre and ganglion cell layers	Neuroglial-like	—
Horniker and Salom (1932)	Retina	Nerve fibre layer chiefly, but ganglion cell and inner molecular layers also involved	Glial cells and nerve fibres	Retinal vascular changes stressed Cystic retinal changes present at distance from nodules
Kuehenmeister (1934)	Retina	All layers	Glial	Calcification and ossification
Fleischer (1935)	Retina	All layers	Glial	Very vascular, calcification and ossification of choroid, isolated areas of choroidal and retino-choroidal atrophy
Messinger and Clarke (1937)	Optic disk	All layers	Glial	Calcification and ossification
Hirose and Nagae (1940)	Optic disk	Nerve fibre layer	Glial	—
Tarlau and McGrath (1940)	Optic disk	Nerve fibre layer	Glial	—
* Loewenstein and Steel (1941)	Optic disk and retina	Nerve fibre layer	Nerve fibres and tumour cells	Retinal detachment and disintegration, small knot-shaped retinal tumours, pyramidal tumour of disk, angiomatous growth at retinal surface, angioma of choroid
Zbinden (1942)	Retina	Nerve fibre layer chiefly, but other layers also involved	Glial	—
Ross and Dickerson (1943)	Optic disk	Nerve fibre layer chiefly	Glial	—
Hall (1946)	Optic disk and retina	Nerve fibre layer chiefly, but ganglion cell and inner nuclear layers also involved	Glial	Choroidal angiomatosis, nodule of abnormal tissue in lens

\* The present writer suggests the possibility of an alternative explanation to that given by Loewenstein and Steel concerning the nature of their case, see note in discussion

shrivelled, the iris extremely atrophic, the choroid ossified, the retina detached and atrophic, and the lens replaced by a bony mass. Finally, signs of malignant degeneration such as the development of intra-ocular metastases (van der Hoeve, 1923*a*, *b*, 1932) or a pseudo-glomatous appearance (Loewenstein and Steel, 1941) may also occur and necessitate enucleation of the eyeball.

Despite the variety of ocular lesions, visual symptoms are unusual, the lesions being for the most part asymptomatic. Sometimes, however, progressive visual failure is the presenting symptom and is due either to the development of optic atrophy secondary to papilloedema (Koch and Walsh, 1939, Guillain and Lagrange, 1934), to optic atrophy associated with a tumour growing at the nerve head (Messinger and Clarke, 1937, Ross and Dickerson, 1943, Sachs and Shaskan, 1944), to the development of a phakoma in the region of the macula (Gifford, 1940), or to a combination of these causes (Seidel, 1938). As already indicated, retinal detachment, opacities of the media, and progressive disintegration of an eyeball may also cause loss of vision of the affected eye, whilst blindness for no apparent cause has also been reported (Ross and Dickerson, 1943).

Histological examination of retinal or disk lesions has been recorded by van der Hoeve, 1923*a*, 1932), Schob (1925), Feriz (1930), Horniker and Salom (1932), Kuchenmeister (1934), Fleischer (1935), Messinger and Clarke (1937), Tarlau and McGrath (1940), Hirose and Nagae (1940), Loewenstein and Steel (1941), Zbinden (1942), and Ross and Dickerson (1943). Their chief findings are summarized in Table I, from which it will be seen that whilst individual variations occur, the lesions described share many features in common. A further account of their structure, based on the examination of the eyes of a patient in whom tuberose sclerosis was associated with melorheostosis (Hall, 1940, 1943), is now presented and is of interest because of the association of retinal and disk lesions with an angiomatous appearance of one choroid and a heterotopous formation in a lens.

#### *Case Report*

*History* The patient, a boy aged 17 years at the time of death, had been under personal observation for 4½ years on account of fits and raised intra-cranial pressure due to tuberose sclerosis. The case has been reported in detail in a previous paper (Hall, 1940). There was no ocular complaint until within a few months of death, when rapid deterioration of vision occurred and he became unable to see to read. Death was due to intra-cranial hypertension resulting from a large paraventricular glomatous tumour associated with widespread cerebral deposits of tuberose sclerosis, the degree of internal hydrocephalus present at autopsy was extreme.

#### *Ophthalmoscopic examination* (Plate 16, Fig 2, Plate 17, Fig 3)

30.3.36 Considerable chronic bilateral papilloedema, no haemorrhages present. There is a small, ill-defined, greyish, non-pulsatile swelling attached to the upper nasal margin of the right optic disk. The left fundus is somewhat obscured by a vertical lobulated opacity within the upper part of the lens.

21 10 37 Intense bilateral papilloedema Approaching the extreme temporal periphery of the left fundus there are two sharply defined whitish-yellow spots while a larger one is present in the periphery of the lower nasal field In addition, there are two larger ill-defined circular lesions and what seem to be numerous vascular naevoid areas at the most extreme temporal periphery, where some of the blood-vessels acquire a whitish streaky outline

TABLE II

*Histological findings of present case*

	Right eye	Left eye
Lens	* Peripheral degeneration	* Peripheral degeneration Small nodular mass in centro of lens
Cornea	* Desquamation of epithelium	* Desquamation of epithelium
Sclera	Normal	Normal
Iris and ciliary body	Oedematous	Oedematous
Choroid	Generalized vascular thickening and fibrosis	Generalized vascular thickening and fibrosis Angiomatous condition also present
Retina	Mass of neuroglial overgrowth at nerve head Oedema of nerve fibre layer 'Absence' of nerve cell layer * ? Autolysis of rods and cones	Neuroglial masses present away from nerve head, originating in nerve fibre layer and causing disruption of nuclear layers beneath Oedema of nerve fibre layer, ? few cells seen in nerve cell layer * ? Autolysis of rods and cones
Optic nerve	Gross atrophy and swelling— ? oedema due to growth at nerve head	Gross atrophy

\* It is suggested that this appearance may be the result of the post-mortem changes which are present

The appearance of the swelling attached to the upper nasal margin of the right disk is unchanged

16 6 38 The optic disks are beginning to show evidence of atrophy

7 3 39 The papilloedema has subsided, the optic atrophy is more apparent, and the patient almost blind

*Post-mortem appearances*

*Right eye* The optic nerve immediately behind the globe is a little swollen and firmer to feel than its fellow This increase in size of the nerve extends up to and involves the papilla, attached to one side of which is a small whitish nodule which projects forwards into the vitreous

*Left eye* Scattered about the retina there are several small discrete whitish-grey nodules, the largest being up to 3 mm in diameter, the intervening retina seems healthy

*Microscopical examination* (Stains used haematoxylin and eosin, haematoxylin and van Gieson, Mallory, Weigert-Pal, Marchi) A summary of the histological findings is given in Table II from which it will be seen that the chief abnormalities are

*Right eye*—a tumour nodule attached to the optic papilla

*Left eye*—several scattered lesions in the retina and one in the lens

Both eyes—choroidal vascular changes and gross atrophy of the optic nerves

*Retinal lesions* All are superficial and arise from the nerve fibre layer, to which the smaller ones are confined (Plate 17, Fig 4) The larger ones are

clearly visible to the naked eye, but the smallest are microscopical in size. The larger ones in places disrupt the inner nuclear layer and in some sections infringe upon the outer nuclear layer, but nowhere is this penetrated though it may be indented (Plate 17, Fig 5). In section the lesions consist of relatively avascular shallow elliptical nodules of tissue composed for the most part of loosely connected cells and fibres whose outlines are often indistinct, giving the general appearance of a reticulated syncytium rich in nuclei of varying size and shape (Plate 18, Fig 6). Nowhere is there any haemorrhage or calcification, and in only one place, in the centre of a nodule, are any lymphocytes to be seen, and here they are distributed around a small blood-vessel. As a rule the lesions are fairly sharply circumscribed and the intervening retina relatively unaffected. In places, however, the distinction between the two is much less abrupt and for some considerable distance away from the lesion the nerve fibre layer continues to show, though to a very much less extent, the structural changes of the nodules themselves (Plate 18, Fig 7). Occasionally the fenestrated appearance of the nodule is accentuated at its periphery, where the many hollow spaces present in between the strands of tissue coalesce to form what seem to be quite large empty multiloculated cysts (Plate 18, Fig 8), but nowhere are these in communication with the vitreous. The arrangement of cells and fibres is most compact at the surface of the larger nodules which are markedly crenated, in sharp contrast to the small ones whose surface is smooth. Moreover, the larger ones are capped by a dense feltwork of closely packed cells and fibres which are often arranged in whorls or brushes (Plate 19, Fig 9). Occasionally a similar but much less compact arrangement of cells and fibres exists at the base of a lesion where elongated cell processes in the form of fine fibres are clearly visible (Plate 18, Fig 8). In some sections the internal limiting membrane is intact over the surface of the nodule, but in others it seems to stop short at the periphery of the lesion. Cells vary as markedly in size as in shape, the only constant feature is their indistinctness of outline. Cells large and small, oval, round, triangular and elongated exist side by side in an irregular manner. Their protoplasm is clear and at times faintly vacuolated. Nuclei vary as much in size, shape, and position as cells, a few of which are multinucleated, containing up to three nuclei. For the most part nuclei stain well, and nucleoli and chromatin tissue are clearly visible. Only an occasional blood-vessel is present. In otherwise unaffected parts of the retina the nerve fibre layer is oedematous, and everywhere there is an almost total absence of the nerve cell layer and widespread disintegration (?autolytic) of the rods and cones.

*Tumour nodule of optic disk.* In section this consists of a small flask-shaped nodule of tissue arising from one side of the optic papilla (Plate 19, Fig 10). Its surface is smooth. It extends laterally for a short distance to terminate abruptly in the nerve fibre layer of the retina, of which it represents a nodular thickening. Its slightly oblique position results in the retina being lifted off the choroid for a short distance and folded upon itself immediately before the two layers make contact (Plate 19, Fig 11). At its base there is a fairly dense basket-work arrangement of cells and fibres which for a short distance infiltrate the papilla, to which the nodule is thereby firmly anchored. Elsewhere the structure of the nodule closely resembles that of the smaller retinal lesions, but it is noticeably more cellular and its meshes are finer (Plate 20, Fig 12). There is, however, the same irregular arrangement of cells and fibres, though in general these are directed longitudinally save on the upper surface of the nodule where they tend to

he vertically. The same tendency to form a syncytium exists as in the retinal nodules. Calcification, haemorrhage, and tissue reaction are again absent, there is no evidence of cyst formation, and only a very occasional blood-vessel is to be seen. Advanced post-neuritic atrophy is present in both optic nerves, the right of which is a little swollen and oedematous as a result of the lesion at the nerve head.

*Choroidal changes* There is generalized vascular thickening and fibrosis present throughout the choroid of both eyes, but in the left eye the choroidal veins are extremely dilated and tortuous, the varicose appearance resembling that of a diffuse angiomatosis.

*Nodule in lens* In section this is seen as a small centrally placed and sharply circumscribed lobulated mass in the anterior fibres of the lens (Plate 20, Fig 13). No definite structure can be determined, but what seem to be the blurred outlines of disintegrated cells and their nuclei are visible in a somewhat granular and deeply staining but otherwise almost structureless matrix which in places shows faint traces of calcification. It is interesting to note that not infrequently the shrunken cells, a few of which are to be found in between the fibres of the lens at a distance away from the main mass of the nodule, lie in what seem to be tiny cyst-like spaces which are sharply defined from the neighbouring tissue.

### Discussion

This case therefore illustrates in a characteristic manner a number of the ocular manifestations of the disorder. The nodule of tissue in the lens is of interest and represents the type of heterotopous formation which occurs in tuberosc sclerosis. Its presence confirms Grinker's (1932) statement that such deposits in the lens do occur in this disorder, but there seems no reason to regard such lesions as a sign of malignancy as van der Hoeve is reported by Grinker to have done. The disk and retinal lesions, particularly the larger retinal ones, in their general appearance and their tendency to have a compact surface layer of cells, separated by a cystic and almost reticular zone from a less compact layer beneath, are almost identical with those described by Schob (1925) and Zbinden (1942) and very similar to those recorded by van der Hoeve (1923a) and Feriz (1930), while the cystic retinal changes at a distance from the nodules correspond closely to those noted by Horniker and Salom (1932). As indicated in the summary of the chief histological findings in these lesions (Table I), it is the general opinion that the tissue of which the nodules is composed is glial in nature and with the aid of special staining methods the presence of intracellular glial fibres has been demonstrated (Schob, 1925, Greenfield, in Messinger and Clarke's case, 1937). In addition, Tarlau and McGrath (1940) in the disk lesion which they examined noted the presence of typical astroblastic glial cells with sucker processes attached to the walls of adjacent capillaries. In his original description of the structure of these lesions, van der Hoeve (1923a) stressed the presence of certain large cells which he called glioneurocytes because he believed that they were descended from the first anlage of the retina, but had not yet differentiated into either glial or ganglion cells. Mann, too, from

her examination of Messinger and Clarke's sections (Messinger and Clarke, 1937) concluded that glial cells of a primitive type were present. She postulated their descent from the first stage (fourth to fifth week) of retinal differentiation, when the cells destined to form the supporting structures of the retina are in process of separating from the primitive neuro-epithelium, and gave her opinion that this differentiation into the specialized glia of the retina had already begun, but had not proceeded very far.

Astroblasts have not been seen nor was it possible in the circumstances which obtained when the eyes were sectioned, to employ special staining methods in the case here recorded, but from the appearance of the lesions they seem in every way identical with those examined and recorded by others. It would, indeed, appear that these lesions represent foci of glial overgrowth, being composed almost entirely of glial cells and fibres of a primitive kind. It may be noted that the whorl-like arrangement of cells and the brush-like areas of gliosis observed in these lesions match exactly the appearance of the cerebral nodules described by Globus (1932), and it will be remembered that these too at times undergo cystic degeneration (Critchley and Earl, 1932), furthermore, the large cells rich in cytoplasm with fine glial processes arising from their bodies are found alike in the retinal as in the cerebral nodules (Grinker, 1932). Grinker was of opinion that these retinal lesions are probably true astroblastic neoplasms of low growth possibilities, but added that as yet enough have not been reported for one to be sure of their classification. Messinger and Clarke (1937), however, concluded that the lesions are hamartomas rather than true tumours. It seems possible to combine these views in the assumption that essentially the lesions are of the nature of hamartomas, but that occasionally they assume the characteristics of a neoplasm of low growth potentiality. Such an assumption seems to reflect the view held by van der Hoeve (1923*b*) that 'All the tumours which we find in tuberosc sclerosis of the brain in different organs are kinds of congenital aberrations. They may be present in the newborn child or appear later. They can be very small and can enlarge to tumefactions, even to real blastomata, which can turn to malignancy'. In this respect the retinal nodules may be compared with the small subependymal cerebral nodules which also very occasionally become neoplastic and develop into the large paraventricular glomatous tumours to which reference has already been made. It may be recalled too that twice (van der Hoeve, 1920, 1923*a*, Loewenstein and Steel, 1941) there was sufficient clinical evidence of malignancy in the affected eye to justify enucleation, that Feriz (1930) also has drawn attention to the occasional development of malignancy in these lesions, that the disk tumour described by Tarlau and McGrath (1940) is known to have developed during adult life, and that the subsequent development of many retinal nodules in an eye in which 16 years previously there had been visible only one such lesion is also on record (van der Hoeve, 1938).

The generalized vascular thickening and fibrosis of the choroid and the

angiomatous appearance of the choroid of the left eye recall the hypertrophy and hyalinization (Globus, 1932) and the dilatations of the blood-vessels sometimes attaining sinusoidal proportions (Critchley and Earl, 1932) which may also be present in the cerebral lesions of this disorder. The presence of vascular involvement in the retinal nodules is stressed by Horniker and Salom (1932) who described very dilated vessels, extensive perivascular changes, and a rich capillary supply to the nodules, these changes they considered to indicate a primary disturbance of the mesoderm. The presence of a small, sharply circumscribed angioma of the choroid was described by Loewenstein and Steel (1941) and their case is all the more remarkable in that in the other eye too there were present extensive retinal changes of an angiomatous nature. As these authors indicated, the presence of such vascular changes in tuberose sclerosis is supporting evidence for the view developed by van der Hoeve in his numerous papers that this disorder and the angiomatoses (the von Hippel-Lindau and the Sturge-Weber syndromes) have much in common with each other, and belong, with neurofibromatosis, to one and the same group of disorders, the so-called phakomatoses. From time to time other instances of this group, showing to a varying degree features common to other members of the group and to other congenital developmental defects, have been recorded, for example, the accepted relationship of tuberose sclerosis with neurofibromatosis, the association of a facial and meningeal vascular naevus with adenoma sebaceum (Greig, 1922), of an extensive vascular naevus of the skin with a true blood-vessel tumour of the brain (Hall, 1934) and with a cerebral (meningeal) haemangioma (Weber, 1929), of a neurofibromatous retinal nodule that histologically resembled the appearance found in both tuberose sclerosis and the von Hippel-Lindau syndrome (van der Hoeve, 1932, 1938), and of a diffuse angiomatous condition of the skin and subcutaneous tissue of a limb in a patient suffering from tuberose sclerosis (Ross and Dickerson, 1943). But the extensive vascular changes and the clinical details described by Loewenstein and Steel are such—and here the present writer is at variance with these authors—that the view may be expressed that in their patient the primary disturbance is equally, if not predominantly, mesoblastic as ectodermal, in other words, it may be suggested that in their patient the disorder is more of the angiomatous than the sclerotic type. Such a view would account for the absence of adenoma sebaceum in their patient, the presence of the intracranial calcification of the Sturge-Weber type, and the unusually pronounced retinal and choroidal vascular changes of the type which occurs in the angiomatoses, clinically and pathologically, in the present writer's opinion, their patient corresponds more to the angiomatous than to the tuberose sclerosis type of disorder. In this connexion it may be recalled that retinal glial proliferations, very similar to those found in tuberose sclerosis, have in fact been observed in association with capillary angiomata of the papilla and retina (van der Hoeve, 1932).

The infiltrative radiological changes in the lungs of Loewenstein and Steel's

(1941) patient are of particular interest and may be of considerable importance, in view of the lung changes that have been recorded in tuberose sclerosis (Berg and Vejens, 1939, Vejens, 1941, Berg and Zachrisson, 1941, Rosendal, 1942, Licht, 1942, Samuelson, 1942, Ackermann, 1944)

### Summary

- 1 The ocular manifestations of tuberose sclerosis are reviewed
- 2 An account is given of the investigation of the eyes of a patient in whom tuberose sclerosis was associated with melorheostosis

It is a pleasure to thank Dr E W Assinder and Professor A M Drennan for their opinions on the sections described Professor Drennan and his department afforded me facilities during my stay in Edinburgh and I gladly avail myself of this opportunity of recording once more my appreciation of the kindness I received Acknowledgements are made also to Mr Norman Dott for introducing me to the Edinburgh Medical Libraries, to the librarians of these institutions for permitting me to consult the volumes under their charge, to Dr T R C Spence and Dr Edith Chalmers, of the Royal Scottish National Institution, Larbert, for allowing me to examine and have painted the fundus oculi of one of their patients, and to Dr F A Pickworth for staining the preparation designed to show the vascular supply of the retinal nodules described in the text The photographs are the work of Mr W J Pardoe, artist and photographer to the Birmingham Medical School.

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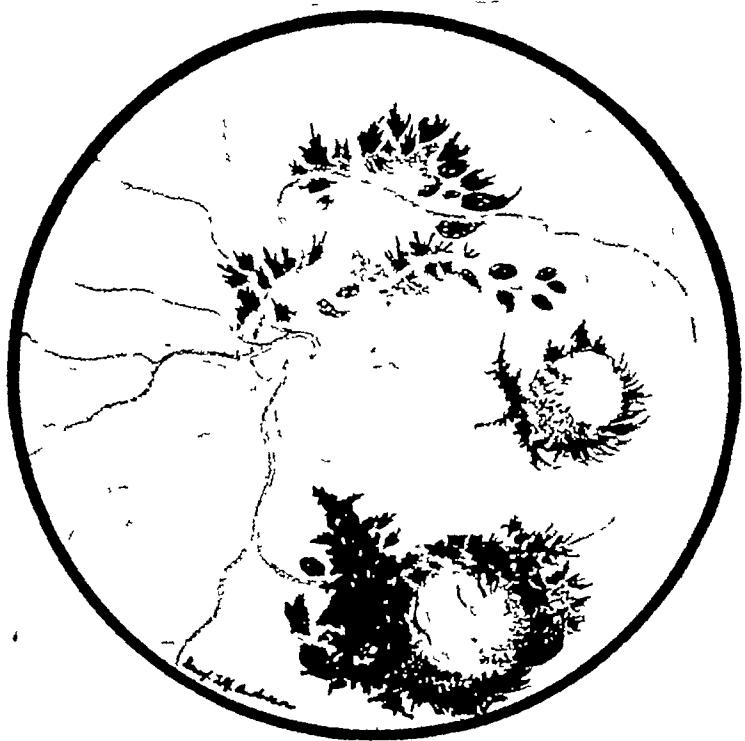


FIG 1 Photograph of ophthalmoscopic painting of retinal and disk lesions associated with profound pigmentary changes described in text the retinal lesions are situate at a much greater distance away from the disk than is represented in the picture

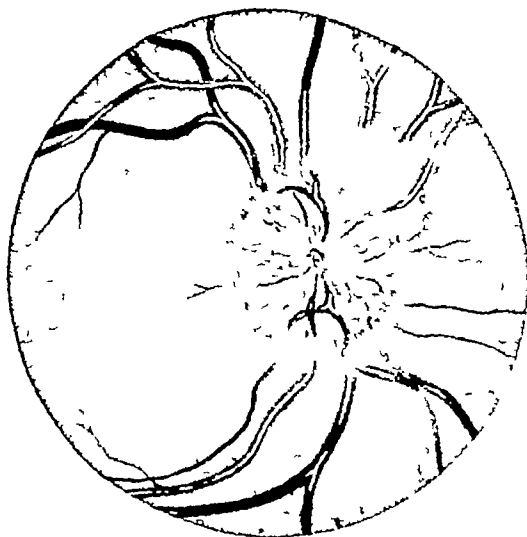


FIG 2 Photograph of painting of right fundus—to show tumour nodule attached to optic disk



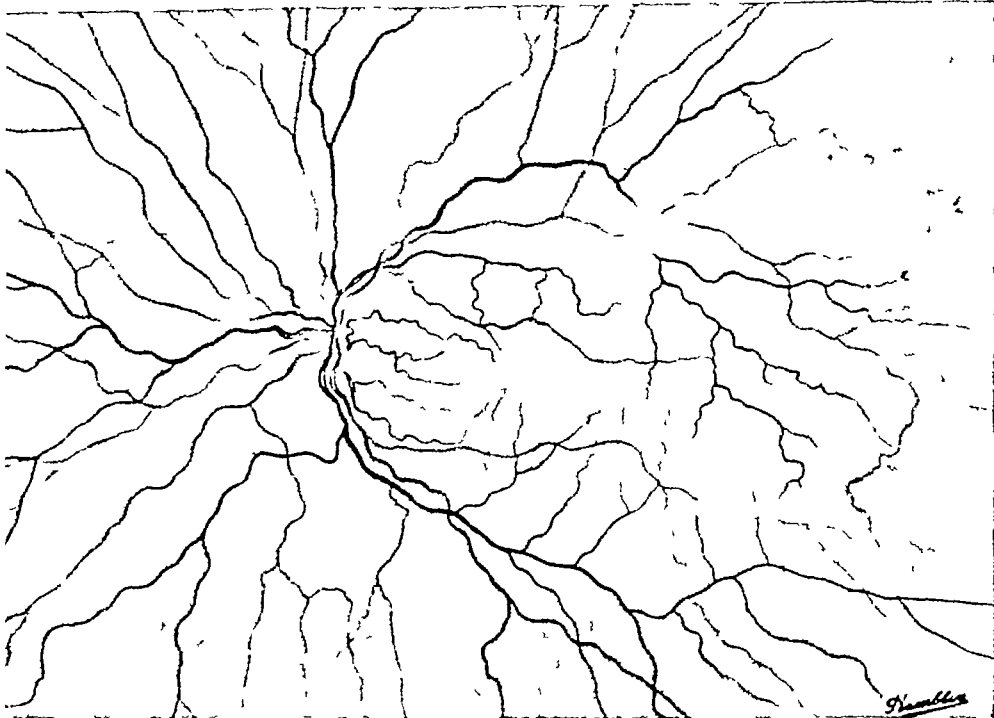


Fig 3 Photograph of painting of left fundus—to show tumour nodules of retina and associated vascular naevoid lesions



FIG 4 Smaller retinal nodule ( $\times 44$ )



FIG 5 Larger retinal nodule ( $\times 33$ ) A more detailed view of the multiloculated cyst (marked with an arrow) at the periphery of the lesion will be found in fig 8



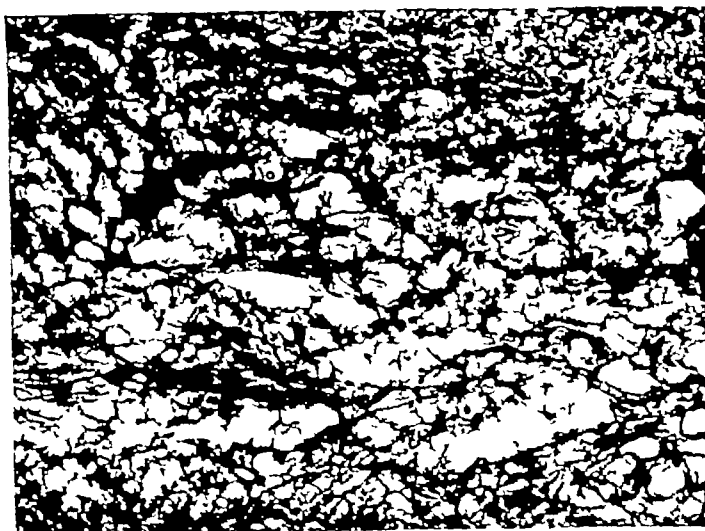


FIG 6 Typical structure of retinal nodule ( $\times 170$ )



FIG 7 State of retina at some considerable distance away from obvious retinal nodule ( $\times 200$ )

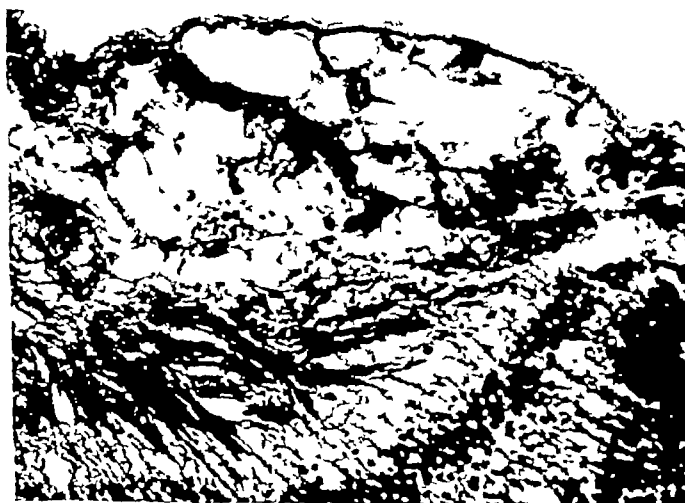


FIG 8 Multiloculated cyst situate at extreme periphery of larger retinal nodule. The brush like arrangement of elongated cell processes is clearly visible ( $\times 170$ )





FIG 9 Typical whorl arrangement of cells in dense feltwork on surface of larger retinal nodule ( $\times 380$ )



FIG 10 Tumour nodule of optic disk ( $\times 44$ )



FIG 11 Retinal fold secondary to oblique position of nodule attached to optic disk ( $\times 44$ )





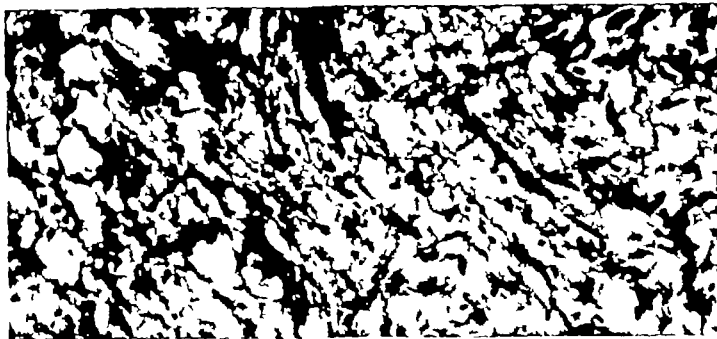


FIG 12 Typical appearance of disk nodule ( $\times 170$ )

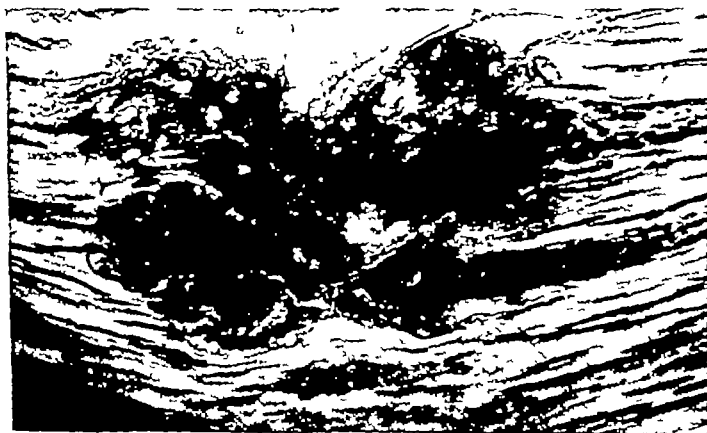


FIG 13 Heterotopous formation in lens ( $\times 170$ )

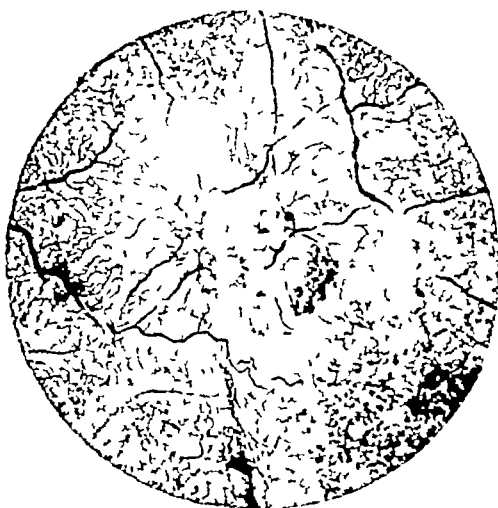


FIG 14 Pickworth preparation, showing relative avascularity of retinal nodule



# THE ESTIMATION OF PROSTATIC PHOSPHATASE IN SERUM AND ITS USE IN THE DIAGNOSIS OF PROSTATIC CARCINOMA<sup>1</sup>

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## *Introduction*

THE human prostate gland contains a large amount of a phosphatase having its optimum activity in acid solution. This enzyme was discovered by Kutscher and Wolbergs (1935) and shown by Kutscher and Worner (1936) to have an optimum range of activity from pH 4.0 to 5.4 when phenyl phosphate was used as substrate. It is not found in the prostate before puberty, and in the normal adult it passes into the semen. The only animal in which it occurs in large amount is the monkey, and then only in the caudal lobe of the prostate. Many other tissues contain acid phosphatase, but the amounts are extremely small in comparison with that found in the prostate. Gutman, Sproul, and Gutman (1936) demonstrated that the prostatic phosphatase is present in malignant prostatic tissue, including the metastatic tumours in bone. Later they found a high acid phosphatase titre in the serum of patients with metastasizing prostatic carcinoma (Gutman and Gutman, 1938). The diagnostic value of this finding has been confirmed by many authors, and a full study of it has been reported by Sullivan, Gutman, and Gutman (1942). In its original form the test is based on the finding of a total acid phosphatase titre higher than that of normal serum. The increases found in prostatic carcinoma, when they occur, vary greatly in degree, some being only slightly above normal and some extremely high. On the other hand, slight increases are occasionally met with in non-prostatic diseases, and although these are uncommon they may, in individual instances, detract from the reliability of the test. For example, a patient may have generalized bone lesions which on radiological examination are consistent with a diagnosis of either osteoplastic metastases or Paget's disease. Clinical examination of the prostate may show no definite enlargement, or an enlargement consistent with simple hypertrophy. Diagnosis then rests entirely on the estimation of acid phosphatase in the serum. If it is very high, there is no doubt of its significance, but if it is only slightly raised a diagnosis of Paget's disease is not excluded. Reliable diagnosis has become more important in view of the value of oestrogen treatment for prostatic carcinoma.

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of filtrate is treated with 1 c.c. of sodium carbonate solution. A control mixture is made with the corresponding amounts of water, phenol reagent, and sodium carbonate solution. The mixtures are incubated at 37°C for five minutes to develop the colour, and read in the Pulfrich photometer with the control mixture in the balance cell, using the filter S72. The instrument is calibrated with a series of standard phenol solutions. The colour is not directly proportional to phenol concentration, and a standard curve is plotted for the readings. The difference between the incubated and non-incubated samples gives the phenol formed by hydrolysis. The unit of phosphatase activity is the liberation of 1 mg. of phenol per 100 c.c. of serum in 1 hour.

#### *Inactivation methods*

*Lability at 37°C* The serum is incubated for 1 hour at 37°C and the acid phosphatase estimated.

*Alcohol-inactivation* To 1 c.c. of serum, 0.4 c.c. of ethyl alcohol is added. The tube is stoppered and the mixture allowed to stand for  $\frac{1}{2}$  hour at room temperature. Water, 0.1 c.c., is added, and a sample of 0.3 c.c. of the opalescent mixture measured into 4 c.c. of buffered substrate for the estimation of acid phosphatase. The volume is corrected by using 1.7 c.c. of phenol reagent after incubation.

*Precautions in regard to the substrate* If the buffered substrate is kept as a stock solution it is liable to undergo spontaneous hydrolysis. The effect of this is to raise the level of preformed phenol in the serum-substrate mixture. Since the phosphatase is estimated from the difference between incubated and non-incubated mixture it is desirable to avoid unnecessarily high levels of preformed phenol. The same percentage error in the estimation of total phenol may cause a much greater error in the phosphatase estimation if the initial phenol level is high. For this reason the substrate is freshly dissolved in the buffer solution for use. It is also important to guard against the growth of organisms in the stock buffer solution, since some organisms yield acid phosphatase.

*The choice of the time of incubation* Gutman and Gutman (1938) recommended three to five hours for sera of normal acid phosphatase titre, and reduced the incubation time for sera of very high titre. This would be legitimate only if the rate of hydrolysis were constant throughout the longer period. The writer has followed the rate of hydrolysis for a number of sera. With sera of normal type the rate is constant at first, but later falls off rapidly until hydrolysis almost ceases. This sharp falling-off occurs at different times with different sera, it is nearly always evident before three hours, and sometimes before two hours. For this reason the incubation time was reduced to one hour. The phenol produced in one hour is sufficient to estimate photometrically even when the acid phosphatase titre is low. The falling-off in hydrolysis on long incubation is due to destruction of the enzyme. This was shown in experiments in which serum, or a prostatic phosphatase preparation, was first incubated in buffer alone for a given period and the substrate then added for estimation of acid phosphatase. The titres found were then lower than before incubation with the buffer. With sera of very

Therefore it seemed desirable to find a method for distinguishing between acid phosphatase of prostatic origin and acid phosphatases derived from other sources. It seemed probable that the prostatic phosphatase was not present in normal serum, since the normal range of titres was the same for men and women. Possible activators or inhibitors of acid phosphatases were therefore considered. Broadly speaking, the acid phosphatases fall into one group in regard to sensitivity to activators and inhibitors, while the alkaline phosphatases also have their group characteristics differing from those of acid phosphatases. The only known specific property of prostatic phosphatase was its irreversible destruction by certain narcotics, including alcohols, described by Kutscher and Worner (1930). The use of alcohol-inactivation as a method of identifying the prostatic phosphatase in serum has been described in preliminary communications (Herbert, 1944, 1945). It was also shown that prostatic phosphatase in serum is destroyed by simple incubation at 37° C. The present paper gives a description of the application of these methods in clinical work. The method depending on alcohol-inactivation is the more specific for prostatic phosphatase, and has alone been adopted as a routine procedure.

### *Methods*

The estimation of acid phosphatase was done by the method of Gutman and Gutman (1938), but as there are some modifications and precautions the technique is described in full.

### *Reagents*

1 *Citrate-hydrochloric acid buffer* A sodium citrate solution is made by dissolving 21.008 gm of citric acid in 200 c.c. of normal caustic soda and making up to 1,000 c.c. in water. The buffer solution is prepared by adding 60 c.c. of N/10 hydrochloric acid to 440 c.c. of citrate solution, and is stored in the refrigerator in a waxed bottle.

2 *Buffered substrate solution* This is a solution of M/200 sodium monophenyl phosphate in the citrate-hydrochloric acid buffer, freshly made as required.

3 *Phenol reagent* The phenol reagent of Folin and Ciocalteu (1927) is diluted 1 in 3.

4 *Standard phenol*, 10 mg per 100 c.c.

5 *Sodium carbonate*, 20 per cent solution, kept warm.

### *Procedure*

Fresh serum must be used, and haemolysis avoided.

*Total acid phosphatase* Two samples are taken, one for estimation of pre-formed phenol and one for estimation of the rate of hydrolysis of the substrate. In each case, 0.2 c.c. of serum is measured into 4 c.c. of buffered substrate in stoppered centrifuge tubes. The first is incubated for exactly 1 hour at 37° C. Proteins are then precipitated by the addition of 1.8 c.c. of phenol reagent, the mixture centrifuged, and the supernatant fluid poured through a small filter (Whatman No. 41 paper). The second sample is precipitated at once without incubation and similarly treated. Of each, 4 c.c.

this rate precisely by taking samples at intervals from the mixture and estimating the phosphatase titre, because when the samples are measured into the buffered substrate solution the alcohol is so far diluted as to have no inhibitory effect on the phosphatase during the stage of its action on the substrate. In such experiments it was found that with a mixture of 1 c.c. of serum and 0.2 c.c. of alcohol the time required for complete inactivation

TABLE I

*Effect of alcohol on prostatic phosphatase in serum*

Experiment	Titre of serum (units)		Titre of serum with added prostatic phosphatase (units)	
	Untreated	Alcohol-treated	Untreated	Alcohol-treated
1	20	18	79	30
2	23	31	34.3	18
	23	31	18.3	28
3	—	42	74.5	33
	—	42	33.5	37
	—	42	17.8	42
4	24	24	131.8	27
	24	24	67.2	27
	24	24	33.6	17

was  $1\frac{1}{2}$  to 2 hours. With 1 c.c. of serum and 0.4 c.c. of alcohol inactivation was much more rapid. This is shown in Fig. 1, the uppermost curve was obtained with serum from a case of prostatic carcinoma, with an acid phosphatase titre of 78 units, and the remaining three curves with sera to which prostatic phosphatase had been added. Inactivation proceeds very rapidly in the first few minutes, it is nearing completion at 15 minutes and at 30 minutes the titre has reached a constant minimum level. Therefore 30 minutes was chosen as the standard time for alcohol treatment, as the minimum necessary to secure the full effect. It will be noted that in the experiment shown in the uppermost curve of Fig. 1, using a serum from a case of prostatic carcinoma, the residual titre after alcohol treatment was above that of normal serum, but was not reduced by prolonging the alcohol treatment. Additional experiments with the prostatic phosphatase added to serum showed that when the mixture was treated for 30 minutes with  $\frac{2}{5}$  volume of alcohol the residual titre did not differ appreciably from the titre of the serum alone (Table I). The difference between the titre of untreated and alcohol-treated serum therefore gives an approximately quantitative measure of the prostatic phosphatase. The acid phosphatase of normal serum is not inactivated by alcohol. The range of variation and normal standards are described later (Table IV). In preliminary experiments a difficulty arose because the inactivation of prostatic phosphatase by alcohol, so clearly shown in serum, was not evident with the prostatic preparations themselves. When prostatic juice was diluted with water, and the solution treated with alcohol, little, if any, inactivation occurred. This raised the question whether the inactivation seen in serum was a truly specific property of the prostatic enzyme or whether it depended on other factors. Alcohol in the quantity



high acid phosphatase titre it is necessary either to reduce the incubation time or to work with diluted serum. Either method gives the same result.

*Avoidance of haemolysis* Corpuseles contain a large amount of acid phosphatase, roughly 100 times the amount in serum (Gutman and Gutman, 1941). Even slight haemolysis therefore introduces appreciable error in the serum titre. The writer has found that the acid phosphatase of corpuseles is

partly destroyed by alcohol under the conditions chosen for inactivation of prostatic phosphatase. King, Wood, and Delory (1945) have also noted this sensitivity to alcohol.

*Conditions for the inactivation of prostatic phosphatase* In the studies which led to the choice of methods for inactivation of prostatic phosphatase, experiments were made with normal and pathological sera, with preparations of the prostatic enzyme, and with the prostatic enzyme added to serum. Preparations of phosphatase from the prostate were made by grinding the finely cut tissue with sand, centrifuging the mixture, and taking off the supernatant fluid. The tissue juice thus expressed contained from 140,000 to 600,000 units of acid phosphatase, and was used in such high dilution for the experimental work that no separation of the enzyme from other constituents was needed. The starting-point of the work was the study published by Kutscher and Worner (1936)

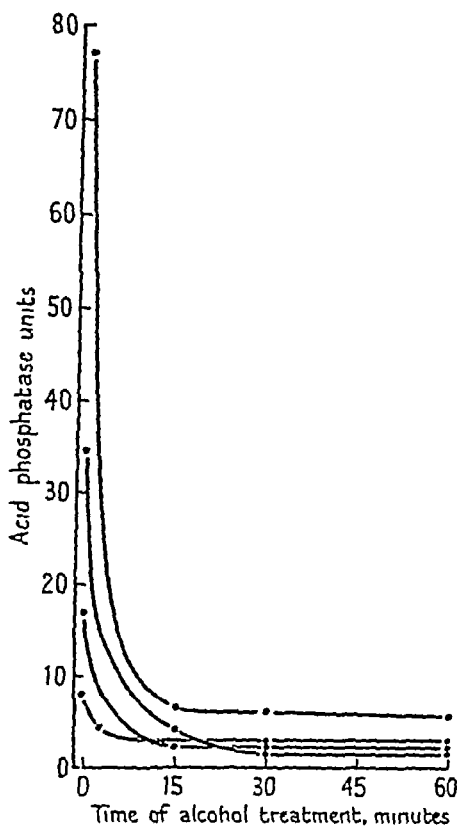


FIG 1 Rate of inactivation of prostatic phosphatase in serum treated with  $\frac{2}{3}$  vol ethyl alcohol at room temperature

They carried out the inactivation with various alcohols at  $37^{\circ}\text{C}$ , and found that in passing up the homologous series the inhibitory effect increased relatively to molar concentration. The higher alcohols are unsuitable owing to their low miscibility with water, so ethyl alcohol was chosen for the present work. It was also found that in serum incubated at  $37^{\circ}\text{C}$  without alcohol the prostatic phosphatase was destroyed, so that for a study of the specific alcohol effect it was necessary to work at room temperature.

*Inactivation of prostatic phosphatase by alcohol at room temperature* Experiments were made on the rate of inactivation of prostatic phosphatase in serum treated with alcohol at room temperature. It is possible to follow

this rate precisely by taking samples at intervals from the mixture and estimating the phosphatase titre, because when the samples are measured into the buffered substrate solution the alcohol is so far diluted as to have no inhibitory effect on the phosphatase during the stage of its action on the substrate. In such experiments it was found that with a mixture of 1 c.c. of serum and 0.2 c.c. of alcohol the time required for complete inactivation

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used causes partial precipitation of serum proteins, but such a non specific effect would not account for the difference between the prostatic phosphatase and the acid phosphatase of normal serum. The possible effect of pH was considered, and experiments were made with prostatic tissue juice diluted in various buffer solutions ranging from pH 4.8 to 7.4 (Table II). Inactivation occurred in all such solutions irrespective of pH. Next a dilution of prostatic

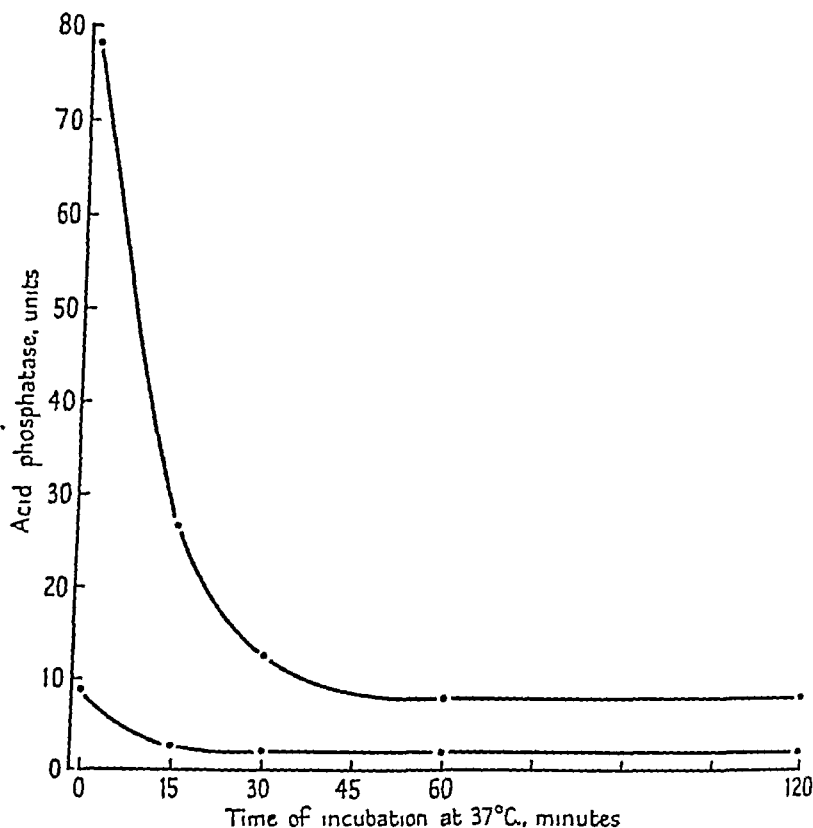


FIG. 2 Rate of inactivation of prostatic phosphatase in serum incubated at 37°C

juice was made in a mixture of sodium chloride and sodium bicarbonate of concentration comparable with serum, and inactivation was observed. In isotonic sodium chloride, without bicarbonate, the effect of alcohol was much less. Inactivation was not quite complete in any of the salt mixtures, but with the sodium salts of weak acids the titre fell to a very low level. It is evident that the effect of serum in facilitating the inactivation of prostatic phosphatase by alcohol is sufficiently explained by the effect of the serum salts, and there remains no objection to interpreting the alcohol inactivation as characteristic of prostatic phosphatase. Further evidence for specificity will be given in describing the clinical use of the test.

*Inactivation by incubation of serum at 37°C.* The lability of the prostatic phosphatase in serum at 37°C was discovered accidentally in the

control experiments made in the study of inactivation by alcohol. Preliminary experiments with normal serum showed that the normal acid phosphatase was not labile at 37° C. It seemed, therefore, that this property might form the basis of a second method of differentiation. The cause of the inactivation has been traced to the pH of serum. When prostatic tissue preparations were diluted in various buffer solutions, it was found that the

TABLE II  
*Effect of alcohol on prostatic tissue phosphatase*

Diluent	Total acid phosphatase (units)	Residual acid phosphatase after alcohol treatment (units)
Water	16.3	12.4
	21.0	16.9
Acetate buffer pH 7.4	23.2	1.4
	16.3	2.7
Citrate buffer pH 4.8	16.3	3.5
pH 5.4	21.0	4.2
pH 5.8	21.0	2.6
pH 6.2	21.0	2.0
pH 6.6	21.0	2.0
Sodium chloride 0.585 %	28.0	2.0
Sodium bicarbonate 0.365 %		
Sodium chloride 0.9 %	21.0	8.0

prostatic phosphatase was destroyed by incubation for one hour at 37° C at pH 7.4. At pH 4.8 and 37° C there was only a slight reduction in titre. These findings are in general agreement with the pH inactivation curves for prostatic phosphatase published by Kutscher and Worner (1936), though under the conditions employed by them inactivation at pH 7.4 was not complete. The rate of inactivation during incubation of serum at 37° C is shown in Fig. 2. Both curves were obtained with sera from patients with prostatic carcinoma. The titre falls rapidly at first and then more slowly, attaining a constant minimum level by one hour. As with the alcohol method, high residual titres are sometimes found, but are not reduced by prolonging the incubation. The application to clinical work is described below and it will be shown that the method is not entirely specific.

#### *Clinical Application*

*Material.* The study covers 87 cases of prostatic carcinoma, 95 cases of prostatic hypertrophy, and 153 other cases including a wide variety of diseases. Total acid phosphatase was estimated in all cases, and differential methods applied in a large proportion. Care was taken to arrive at a reliable diagnosis based on clinical, radiological, and histological evidence, independently of acid phosphatase titres. In a few cases diagnosed as prostatic carcinoma, with bone metastases and without clear evidence of the primary growth in the prostate, the finding of a high acid phosphatase in the serum was the basis of diagnosis in the first instance, and the subsequent response to oestrogen treatment, both in regression of tumours and fall in serum acid

phosphatase, was taken as confirming the diagnosis. Consideration of the evidence in the whole series in which prostatic carcinoma was diagnosed showed that the mere finding of a high acid phosphatase titre cannot have biased the diagnosis in more than five cases. On the other hand, in a few cases the diagnosis of metastasizing prostatic carcinoma has been accepted on clinical and radiological evidence alone, in spite of a normal acid phos-

TABLE III

*Total acid phosphatase in pathological sera*

Diagnosis	Total cases	Number of cases with acid phosphatase in the range													Over 100 units
		1 to 2	2 to 3	3 to 4	4 to 5	5 to 6	6 to 8	8 to 10	10 to 15	15 to 20	20 to 25	25 to 50	50 to 75	75 to 100	
Carcinoma of prostate with bone metastases	35	—	3	1	2	1	6	1	3	4	—	4	4	2	4
Carcinoma of prostate, no bone metastases demonstrable	47	6	9	12	8	2	2	4	1	2	—	1	—	—	—
Carcinoma of prostate, no radiological examination	5	1	1	—	2	—	—	1	—	—	—	—	—	—	—
Senile hypertrophy of prostate	95	12	51	23	7	1	—	1	—	—	—	—	—	—	—
Paget's disease of bone	22	3	8	7	2	—	2	—	—	—	—	—	—	—	—
Parathyroid osteitis	2	—	—	1	—	—	1	—	—	—	—	—	—	—	—
Miscellaneous bone diseases	23	3	8	8	3	1	—	—	—	—	—	—	—	—	—
Hepatitis or cirrhosis hepatis	19	2	1	2	7	4	3	—	—	—	—	—	—	—	—
Obstructive jaundice	4	—	—	3	—	1	—	—	—	—	—	—	—	—	—
Nephritis	16	4	3	4	3	2	—	—	—	—	—	—	—	—	—
Miscellaneous (general)	66	19	23	23	1	—	—	—	—	—	—	—	—	—	—

TABLE IV

*Inactivation methods in non-prostatic diseases*

Change in acid phosphatase titre (units)	Number of sera showing this change	
	After alcohol treatment	After incubation at 37°C
More than -2.0	0	2
-2.0 to -1.6	0	1
-1.5 to -1.1	2	3
-1.0 to -0.6	13	11
-0.5 to +0.5	64	21
+0.6 to +1.0	14	1
+1.1 to +1.5	3	1
+1.6 to +2.0	2	1
More than +2.0	4	0
Total cases	102	41
Mean change	+0.17 unit	-0.37 unit

phatase titre. Eighteen cases of prostatic enlargement with normal serum acid phosphatase have been excluded owing to uncertain diagnosis. The series includes 22 cases of Paget's disease of bone. In eight of these there was some prostatic enlargement diagnosed as non-malignant. Of these, two were proved histologically to have benign hyperplasia, five were followed for eight to 12 months without any sign of malignancy, and in only one did the diagnosis rest on the original clinical examination alone.

*Results*

The results are shown in Tables III to VI. In Table III are summarized the data for total acid phosphatase in serum in the whole series of cases. Table IV summarizes the results of alcohol treatment and of incubation at 37°C in non-prostatic diseases, which form the basis of definition of the normal findings with these methods. In Table V are collected the details

TABLE V

*Non-prostatic diseases with total acid phosphatase above five units*

Diagnosis	Sex	Acid phosphatase		
		Untreated serum	Alcohol-treated serum	Serum incubated for 1 hr at 37°C
Parathyroid ostentis	F	6.2	—	6.7
Paget's disease	F	6.8	6.8	—
" "	F	6.2	6.2	—
Gastric carcinoma with bone metastases	M	5.8	6.8	—
Nephritis	M	5.8	5.0	5.2
"	F	5.2	5.0	4.0
Gallstones	F	5.5	5.5	5.5
Hepatitis	F	6.7	7.8	4.5
"	M	5.4	4.8	4.8
"	M	6.3	6.1	6.3
"	M	5.6	2.4	—
"	M	5.5	4.9	—
"	M	5.6	5.2	—
"	M	5.6	5.0	—
Subacute liver necrosis	F	6.5	6.5	—

of those non-prostatic diseases in which the total acid phosphatase was definitely above normal. Table VI shows the full details of those cases of prostatic carcinoma in which inactivation methods were applied.

*Non-prostatic diseases* In assembling the data for total acid phosphatase in 153 sera it was noted that the higher titres occurred more frequently in diseases of the skeleton, liver and bile passages, and kidneys than in other diseases. For this reason the non-prostatic diseases are divided into groups in Table III, and the definition of the normal is based on a general miscellaneous group from which these special diseases are excluded. On this basis the usual normal range is from 1 to 4 units and the extreme range 1 to 5 units. The normal thus defined is slightly higher than that given by Sullivan, Gutman, and Gutman (1942), the difference is accounted for by the shorter incubation time used in the present work.

In cancer of organs other than the prostate, without bone metastases, there are no abnormalities, and 21 such cases are included in the 'general miscellaneous' group. In secondary carcinoma of bone, with the primary growth in organs other than the prostate, there is a slight tendency to high values, though no more than in other generalized bone diseases. The group of 'miscellaneous bone diseases' includes 11 cases of secondary carcinoma of which two gave titres above 4 units.

TABLE VI

*Acid phosphatase in prostatic carcinoma*

[ 230 ]

Case	Bone metastases	Histology	Acid phosphatase (units)			Alkaline phosphatase (units) (Jenner and Kay, 1932*)	Duration of oestrogen treatment	Remarks
			Untreated serum	Alcohol-treated serum	Serum incubated at 37° C			
1	Present	—	167.0	—	3.1	—	None	—
2	Present	—	142.0	4.4	—	26.3	None	—
3	Present	—	93.5	8.3	9.8	82.2	None	Bedridden
			52.0	4.8	5.3	68.4	9 days	—
			49.8	4.6	5.6	111.6	3 weeks	—
			16.2	4.8	5.0	90.5	10 weeks	—
			11.5	3.5	—	83.3	14 weeks	—
			13.9	7.0	—	72.0	18 weeks	—
			9.5	6.0	—	47.0	5 months	Sclerosis of metastases in X-ray films Well and walking
			10.9	4.7	—	56.0	6 months	—
			8.7	4.9	—	72.3	7 months	—
			6.5	4.0	—	43.2	8 months	—
			7.6	4.9	—	52.0	9 months	Extension of metastases and clinical relapse
			9.0	5.2	—	22.5	12 months	Urinary symptoms for first time In bed
			7.0	3.5	—	13.1	17 months	Better, but in bed
4	Present	—	5.9	2.6	—	—	20 months	—
5	Present	—	85.0	3.5	—	36.0	None	—
			74.3	2.5	—	13.4	None	—
			2.2	1.0	—	12.1	1 month	—
			2.3	2.0	—	9.0	2 months	—
			2.6	3.4	—	7.0	3 months	—
6	Present	—	66.1	8.3	—	58.4	None	—
7	Present	Adeno carcinoma	39.0	7.6	6.1	—	None	—
8	Absent	—	27.6	3.7	—	—	None	—
			14.6	3.9	—	—	7 days	—

9	No examination	Small solid strands of carcinoma cells	27 5	4 2	4 5	58 8	None 6 days	—
10	Present	Adeno-carcinoma	16 5	2 5	2 5	41 2	None	—
11	Present	—	25 9	4 3	—	—	None	—
			19 5	4 1	4 6	21 0	2 months	—
			5 3	4 2	2 9	11 4	11 months	Dong well, regression of metastases in lymph nodes
			6 9	3 1	—	11 3		
12	Absent	—	17 7	2 9	—	—	None	—
13	Absent	—	16 9	—	—	—	None	—
			11 0	3 0	2 2	—	1 day	—
			7 2	2 6	2 5	—	6 days	Died of cardiac infarct after one month's treat- ment
			4 0	2 2	1 9	—	11 days	
14	Present	—	15 5	4 2	4 2	—	None	Bedridden
			4 5	2 5	2 6	45 0	10 days	Good clinical response
			2 7	2 5	2 7	68 1	17 days	—
			4 9	3 8	—	84 6	6 weeks	—
			5 0	4 7	—	56 5	3 months	Sclerosis of metastases in X-ray films
			3 0	3 0	—	40 0	4 months	—
			3 9	2 5	—	19 8	6 months	—
			4 9	2 6	—	7 8	7 months	Rather more backache, otherwise well
15	Present	Adeno carcinoma	7 5	3 5	—	21 7	9 months	—
16	Present	—	7 2	1 9	—	42 1	11 months	—
17	Present	Rather anaplastic carcinoma	15 3	3 7	—	—	None	—
			14 9	4 1	3 8	14 2	None	—
			14 1	—	—	—	None	—
			5 0	3 2	—	—	3 weeks	—
18	Present	—	11 2	4 4	—	93 6	None	—
19	Absent	Adeno carcinoma	9 3	3 8	4 0	—	None	—
20	Absent	—	8 8	2 9	1 7	—	None	—
21	Present	—	8 3	4 7	5 0	28 5	None	—
			7 2	4 0	3 0	—	None	—
			5 7	3 3	4 0	—	10 days	—
			4 1	2 9	—	—	3 months	Greatly improved
			3 2	2 4	—	—	6 months	Still well

\* The normal alkaline phosphatase of plasma by the Jenner and Kay method is 3 to 8 units



TABLE VI (continued)

Case	Bone metastases	Histology	Acid phosphatase (units)			Alkaline phosphatase (units) (Jonner and Kay, 1932*)	Duration of oestrogen treatment	Remarks
			Untreated serum	Alcohol-treated serum	Serum incubated at 37° C			
22	No examination	—	81	33	29	—	None	—
23	Present	Adeno-carcinoma	80	23	25	—	None	—
24	Present	Moderately differentiated adeno carcinoma	77	63	—	—	None	—
25	Present	—	75	53	—	—	None	—
26	Present	—	74	42	—	—	None	—
			34	25	—	—	5 days	—
27	Absent	—	37	37	—	—	12 days	—
28	Absent	Mainly adeno carcinoma, partly anaplastic	71	22	—	—	None	—
			51	45	—	—	None	—
29	Absent	Adeno-carcinoma	48	35	—	—	None	—
30	No examination	—	46	31	—	—	None	—
31	Absent	—	19	17	—	—	6 months	—
32	No examination	Adeno carcinoma	45	38	30	—	None	—
		Adeno carcinoma	45	27	22	—	1 day	—
33	Absent	—	17	20	15	—	2 days	—
34	Absent	—	43	30	38	—	None	—
35	Present	—	43	40	—	—	None	—
			43	34	—	—	1 day	—
36	Present	—	51	43	—	—	4 weeks	—
37	Absent	Well differentiated adeno-carcinoma	27	33	—	—	7 weeks	—
		Adeno-carcinoma	40	43	—	—	None	—
38	Absent	—	40	46	34	—	None	—
39	Absent	Adeno-carcinoma arising in a hyperplastic gland	38	35	—	—	None	—
		Adeno-carcinoma	36	27	—	—	None	—
40	Absent	—	35	34	—	—	None	Good response to stilbo- estrol later

41	Absent	Adeno-carcinoma	35	21	—	—	None	—	Diagnosis clinically de- finite
42	Absent	—	33	30	—	—	None	—	
43	Absent	—	32	26	—	—	None	—	
44	Absent	Adeno-carcinoma	32	15	—	—	None	—	
45	Absent	Adeno-carcinoma	32	32	—	—	None	—	
46	Present	—	30	28	—	—	None	—	
47	Present	—	29	38	—	—	None	—	
48	Absent	—	28	20	—	—	None	—	
49	Absent	Carcinoma	27	28	—	—	None	—	Diagnosis clinically de- finite
50	Absent	Adeno-carcinoma	27	29	—	—	None	—	
51	Present	Anaplastic carcino- ma	27	25	—	—	None	—	
52	Absent	—	26	24	—	—	None	—	
53	Absent	Anaplastic carcino- ma	24	22	—	—	None	—	
54	Absent	Well differentiated adeno-carcinoma	20	32	—	—	None	—	
55	No examination	—	20	20	—	—	None	—	
56	Absent	Adeno-carcinoma	16	09	20	—	None	—	

\* The normal alkaline phosphatase of plasma by the Jenner and Kay method is 3 to 8 units

Paget's disease of bone seems no more liable to be associated with high serum acid phosphatase than other bone diseases, only four cases out of 22 gave titres above 4 units and only two cases were distinctly high (Tables III and V). It is noteworthy that in the two cases of Paget's disease with serum acid phosphatase above 5 units, the serum alkaline phosphatase was extremely high (167 and 185 units by the Jenner and Kay method). Yet there is no close correlation between acid and alkaline phosphatases in bone diseases. Another case of Paget's disease with a serum alkaline phosphatase of 79.4 units had an acid phosphatase of 3.0 units, another showed alkaline phosphatase 69.6 units and acid phosphatase 3.4 units. Also, the case of secondary bone carcinoma listed in Table V, with acid phosphatase 5.8 units, had an alkaline phosphatase of 44.3 units. There is a possibility that with very high alkaline phosphatase titres the activity of the phosphatase derived from bone may show itself slightly at the acid reaction also, but the figures cited show that if any such effect occurs it must be very small, probably at most 2.5 units of 'acid phosphatase' corresponding to 100 units of alkaline phosphatase. In view of the variation in serum acid phosphatase derived from normal sources one would not expect that interference by alkaline phosphatase, if it occurs, would be recognizable from a correlation between acid and alkaline phosphatase titres. The proportion of abnormal acid phosphatase titres found in the present series of cases of Paget's disease is about the same as that found by Sullivan, Gutman, and Gutman (1942) in a series of 96 cases, and lower than that found by Watkinson, Delory, King, and Haddow (1944) in a series of nine cases.

The most striking incidence of high titres occurs in diseases of the liver, specially hepatitis and hepatic necrosis. The group of 19 cases listed in Table III is composed of five cases of cirrhosis and 14 cases of hepatitis or hepatic necrosis. Only two cases of hepatitis had titres below 4 units and seven had titres above 5 units.

The results of inactivation methods applied to sera from non-prostatic diseases are shown in Table IV. Alcohol treatment usually causes no significant change in acid phosphatase activity, it sometimes causes a definite rise and in a minority of cases apparently a slight fall. Where the change in titre is no more than 0.5 unit in either direction the results are regarded as within the range of technical error, and possibly the extreme range of error may account for differences up to 1 unit. Rises as a result of alcohol treatment seem to have no special significance. The normal standard adopted on the basis of 102 sera is that alcohol treatment does not cause a fall of more than 1 unit. There are only two exceptions to this rule, and if in routine practice a suspicious fall is encountered, a repetition of the test will settle the point.

The method of incubating the serum at 37°C has not given such clear-cut results. Though a large proportion of sera show no change, the results are more irregular than with the alcohol method, and six cases out of 41 show falls of more than 1 unit. When these results had been obtained the test was abandoned as a routine procedure, but it may sometimes be of use. A

fall in titre on incubation does not prove the presence of prostatic phosphatase, but the absence of a fall would be a useful negative finding

From the diagnostic point of view it is important to establish that the behaviour of phosphatases derived from sources other than the prostate is the same whether the total acid phosphatase titre is normal or raised. Presumably the normal acid phosphatase of serum is a mixture derived from various tissues, and if in pathological conditions any one of these sources predominates sufficiently to raise the total titre above normal, any special properties of the phosphatase concerned might then become apparent. Of a total of 153 sera from non-prostatic diseases only 14 had titres above 5 units, and these are collected in Table V. They conform to the rule that alcohol treatment never causes a fall of more than 1 unit, and sometimes causes a distinct rise. They also illustrate the unreliability of the method of incubating the serum at  $37^{\circ}\text{C}$ , which caused falls of more than 1 unit in two cases out of seven.

*Prostatic hypertrophy* The total acid phosphatase of the serum has been estimated in 95 cases of benign hyperplasia of the prostate (Table III). Of these, the diagnosis was histologically confirmed in 56 cases. The method of alcohol treatment has been applied in 68 cases of this group, and the method of incubating the serum at  $37^{\circ}\text{C}$  in 15 cases. With the exception of five cases, the results were the same as those found in non-prostatic diseases, both in regard to total acid phosphatase and in the absence of inactivation by alcohol. Incubation at  $37^{\circ}\text{C}$  also gave the same results as in non-prostatic diseases. The results as a whole therefore confirm those of earlier workers, that in benign hyperplasia the prostatic phosphatase does not pass into the blood-stream. There is no reason why it should do so, as the anatomical relations between prostatic tissue cells and blood-vessels are not disturbed. Possibly operative trauma, trauma by catheters, or inflammatory lesions might temporarily open up communication between the cells and the blood-stream, but the histories of the five exceptional cases showed no definite correlation between trauma and the presence of prostatic phosphatase in serum. In all five cases the diagnosis was histologically confirmed, but as the biopsy material was obtained by endoscopic resection the diagnosis is strictly valid only for the portions examined. In three of the five cases the total acid phosphatase of serum was normal, but there was a fall of more than 1 unit after alcohol treatment. In each case this was a single observation, and in two of the three cases the test was repeated and a normal result obtained. In the fourth case, admitted with gross retention of urine, the figures for acid phosphatase were 5.4 units in untreated serum and 3.0 units after alcohol treatment. Eighteen days later, after relief of obstruction by suprapubic cystostomy, the acid phosphatase was 2.9 units, not reduced by alcohol treatment. In the remaining case, three acid phosphatase estimations were made within four days. The results were: first day, untreated serum 3.5 units, second day, untreated serum 8.8 units, alcohol-treated serum 2.4 units, fourth day, untreated serum 5.2 units, alcohol-treated serum 4.0 units.

Incubation of the serum at 37° C also showed the fall in titre. The patient was seen again 10 months later, when there was no clinical evidence of malignancy and the serum acid phosphatase was normal both in total titre and in the absence of inactivation by alcohol or by incubation.

*Prostatic carcinoma* The results for total acid phosphatase in serum in 87 cases of prostatic carcinoma are shown in Table III. Titres above 5 units occurred in 29 out of 35 cases with bone metastases, and in 12 out of 47 cases without bone metastases. The extent of metastases in soft tissues is not known. Alcohol treatment was applied in 56 cases of prostatic carcinoma, and the results for these are given in Table VI. Data illustrating the effects of oestrogen treatment on the acid and alkaline phosphatase are included. In Table VI the cases are arranged in descending order of the initial acid phosphatase titre. In those numbered 1 to 27 the acid phosphatase was high when the patients were first seen. Without exception, alcohol treatment lowered the titre, usually to the normal level. In a few cases the residual activity after alcohol treatment was above normal. When the same sera were subjected to alcohol treatment and to incubation at 37° C, the residual activity was usually almost the same by both methods. In the remaining 29 cases the total acid phosphatase was normal, but among these there were five cases in which a significant fall in titre occurred after alcohol treatment (Nos 29, 30, 32, 41, and 44). In view of the extreme rarity of such results in diseases other than prostatic carcinoma, these observations suggest that the alcohol method makes it possible sometimes to detect the prostatic phosphatase, and thus to obtain evidence for suspecting prostatic carcinoma, even when the total acid phosphatase is not significantly raised. Caution is necessary in interpreting such results, because, when the total titre is low, one is working close to the margin of experimental error, but if the sensitivity to alcohol is repeatedly found in any individual case the possibility of malignancy should be seriously considered.

In patients treated with synthetic oestrogens (usually stilboestrol) prostatic phosphatase, if originally present, decreased, and often entirely disappeared. Among the treated cases there are some instances in which alcohol-sensitivity was still evident when the total acid phosphatase had returned to normal. This is seen in Case 13 at 11 days and in Case 21 at three months, and at several stages in the progress of Case 14. The last case is specially interesting in showing the independent variation of the prostatic and non-prostatic fractions of the serum acid phosphatase. Probably one cannot sharply separate the two fractions. It has already been shown that prostatic phosphatase is completely destroyed under the conditions of the alcohol method, but as the activity of the non-prostatic fraction may sometimes be slightly increased by alcohol, it is possible that in some sera the prostatic fraction may be underestimated if it is calculated simply as the difference between treated and untreated serum. In Case 14 the clinical result was good improvement up to seven months and then a partial relapse. The alkaline phosphatase figures reflected this. In the early stages the originally high alkaline phos-

phatase rose still farther, an effect which has been described by other workers and is interpreted as evidence of osteoblastic activity associated with healing (Huggins and Hodges, 1941, Chute and Willetts, 1942, Watkinson, Delory, King, and Haddow, 1944) In accordance with this view, the next radiological examination showed sclerosis of the metastatic bone lesions Later the serum alkaline phosphatase steadily fell to normal, but from the seventh to eleventh month of treatment rose again This secondary rise suggested further extension and occurred when the patient suffered rather more from backache The prostatic fraction of the serum acid phosphatase fell greatly in the first 10 days, then disappeared, and apart from a possible return at six weeks remained absent until six months, when it was again recognizable in spite of a normal total acid phosphatase titre It then continued to increase and in the latest observations was sufficient to raise the total titre above normal In this case the reappearance of the prostatic phosphatase seemed to be the first sign of a partial relapse On the other hand, in Case 3, in which the prostatic phosphatase never entirely disappeared, there was a partial relapse not clearly reflected in either acid or alkaline phosphatase values

### *Discussion*

The present work confirms both the value and limitations of the estimation of total acid phosphatase in serum as a diagnostic test The introduction of the alcohol-inactivation technique is a useful refinement which assists the interpretation of results when the total titre is not high enough to be in itself diagnostic of prostatic carcinoma In patients suffering from urinary obstruction of such degree as to require immediate surgical relief, diagnosis will usually be made by biopsy, but in a number of cases dissemination of the growth occurs before the primary tumour has advanced sufficiently to cause urinary obstruction In others the urinary obstruction may not be an urgent symptom, and if the diagnosis is established, surgical intervention may be unnecessary as the obstruction may be relieved by oestrogen treatment Clinical examination may make the diagnosis certain if there is considerable local invasion, but in many cases the clinical findings cannot establish the diagnosis Therefore there are many cases in which the diagnosis may rest mainly on the estimation of serum acid phosphatase The diagnostic value of the test is limited by the fact that prostatic phosphatase is not always found in the serum in prostatic carcinoma, though it is nearly always found when there are metastases in bone The frequency of high values reported in the literature is shown in Table VII, in which the figures in each paper are interpreted by the authors' own normal standards.

As has been pointed out by Sullivan, Gutman, and Gutman (1942), the extent of transference of the prostatic phosphatase from the malignant tissue to the circulation must depend partly on the extent of invasion of blood and lymph channels, and partly on the rate of production of the phosphatase in the tumour tissue Therefore, in general, a widely metastasizing

growth is likely to yield most phosphatase to the blood-stream, but there are exceptions to this rule in all the available reports. Some of these may be due to wrong diagnosis, but not all. The remainder may be explained either by lack of production of phosphatase by the tumour when it is of the anaplastic type, or by anatomical conditions such that the tumours in fact invade blood-vessels less than would be expected from their wide distribution.

TABLE VII

*Acid phosphatase of serum in prostatic carcinoma*

	All cases		Cases with bone metastases		Cases without bone metastases	
	Total number	Number with high titres	Total number	Number with high titres	Total number	Number with high titres
Huggins and Hodges (1941)	47	21	25	19	20	1
Huggins, Stevens, and Hodges (1941)	14	7	—	—	—	—
Sullivan, Gutman, and Gutman (1942)	200	126	130	115	70	11
Watkinson, Delory, King, and Haddow (1944)	10	6	7*	6	3	0
Herger and Sauer (1941)	31	22	—	—	—	—
Herger and Sauer (1945)	—	—	59	52	—	—
Smith and MacLean (1943)	10	7	5	3	5	4
Present paper						
Total phosphatase	87	42	35	29	47	12
Differential method	56	32	24	20	26	8

\* Including two cases in which carcinoma of the prostate was associated with bone lesions diagnosed as Paget's disease

Both explanations were required to account for the findings of Sullivan, Gutman, and Gutman (1942). In some of their cases with metastases and without rises in serum acid phosphatase the tumour was known to be of the anaplastic type, and in one case they proved that the tumour tissue did not contain the phosphatase. In other instances the serum acid phosphatase, which had been normal when the patient was first seen, in spite of the presence of metastases, rose at a later stage, showing that the tumours were producing the enzyme.

In the present study there were six instances of serum acid phosphatase less than 5 units in cases with bone metastases (Table III). Unfortunately histological examination was made in only one of these (Case 51, Table VI), and in that case the tumour was anaplastic. In two of the remaining cases the diagnosis was not certain. In one other, the tumour was certainly of a type to produce the prostatic phosphatase because it rose very high later, and the history suggests the importance of invasion of large vessels. When this patient was first seen there were bone metastases and the serum acid

phosphatase was 43 units. Work with inactivation methods had not begun at this time. The patient responded very well to stilboestrol treatment, after 18 months' treatment he was in good condition and the radiological examination showed a most dramatic disappearance of many of the lesions in the pelvis and lumbar spine. Soon after this he relapsed, and after another five months was very ill, though the radiological picture in the pelvis and lumbar spine showed no deterioration. The serum acid phosphatase was 281 units. A few days after this observation he died at his home, and his doctor's diagnosis was cerebral haemorrhage. The story suggests that a cranial metastasis may have eroded a cerebral vessel, and caused massive transference of the prostatic phosphatase to the circulation at a time when the vessel was about to break down. As there was no autopsy this interpretation could not be confirmed, but it is evident that whenever a large vessel is involved the rise in serum acid phosphatase will be determined by the relation of such a vessel to the local tumour rather than by the general distribution of metastatic lesions.

In the cases in which the prostatic phosphatase is continuously present in the serum, the transference of phosphatase from tumours to blood-stream must proceed continuously at a rapid rate. It has been shown that at the natural pH of serum, and at body temperature, the prostatic phosphatase is rapidly destroyed, and this effect presumably occurs *in vivo*. The titre in any serum must be maintained as a balance of continuous inflow and destruction, and the upper curve of Fig. 2 shows that the rate of destruction is more rapid when the titre is high. In that example, with an initial titre of 78 units, 50 units were destroyed in 15 minutes. This implies that in order to maintain a titre of 78 units per 100 c.c. of serum the inflow from tumour cells must be at least 200 units per 100 c.c. of serum per hour. This is not a surprising rate of inflow in view of the fact that prostatic tissue juice may contain as much as 600,000 units per 100 c.c., at that figure it would be sufficient for the contents of 1 c.c. of tissue juice to pass into the total circulation (3,000 c.c. of plasma) every hour. This recognition of a dynamic balance of inflow and destruction may have a bearing on the investigations of therapeutic agents. The time required for a fall in serum acid phosphatase when the growth and activity of the tumour cells is inhibited would depend upon several factors. The first factor, disappearance of the phosphatase in circulation when the supply is cut off, can be assessed, it would occur within an hour if the supply were suddenly stopped. The next factor involved is the rate of destruction of acid phosphatase in the tissue itself when the cells cease to produce it. That is unknown, but is presumably rapid, judging from the speed of response to orchidectomy. One case early in the present series was treated by orchidectomy, in four days the serum acid phosphatase fell from 79 to 26 units, and such a quick response suggests that this early fall is due more to an inhibition of the metabolic activity of the cells than to cessation of cell multiplication or closure of the communications between tissues and vessels. The response to



stilboestrol is slower than the response to orchidectomy. With either treatment there is at a later stage anatomical regression of the tumours as well as inhibition of metabolic activity. In patients showing a high serum acid phosphatase the fall under treatment is the earliest objective sign that the tumours are sensitive to oestrogens. Therefore it is desirable that in all cases the acid phosphatase should be estimated before treatment begins.

### *Summary*

1 A study of the diagnostic use of estimations of serum acid phosphatase has been made on the basis of 87 cases of prostatic carcinoma, 95 cases of prostatic hypertrophy, and 153 cases including a wide variety of diseases.

2 The total acid phosphatase titre is raised in the great majority of cases of prostatic carcinoma with metastases in bone and in a small proportion of cases without demonstrable bone metastases. The abnormally raised titres vary from 5 to 281 units on the scale of Gutman and Gutman (1938). In a small proportion of non-prostatic diseases minor rises above normal are encountered.

3 In order to assist diagnosis in those cases in which the serum acid phosphatase is only slightly raised, methods of inactivation of prostatic phosphatase have been studied.

4 Prostatic phosphatase in serum is inactivated either by incubation of the serum for one hour at  $37^{\circ}\text{C}$  or by treatment of the serum with 2/5 volume of ethyl alcohol for  $\frac{1}{2}$  hour at room temperature.

5. The method of incubation of the serum at  $37^{\circ}\text{C}$  is not recommended as a routine diagnostic test. Prostatic phosphatase is regularly inactivated. In the majority of sera from non-prostatic diseases the acid phosphatase is not inactivated, but exceptions are sufficiently frequent to make the test unreliable.

6 Inactivation by alcohol at room temperature gives a specific test for prostatic phosphatase and an approximately quantitative measure of the prostatic fraction of the acid phosphatase. It clearly distinguishes between raised titres due to the presence of prostatic phosphatase, and raised titres of different origin. It may sometimes make it possible to detect prostatic phosphatase even when the total titre of the serum is not raised.

I wish to express my thanks to the Honorary Physicians and Surgeons of the Royal Victoria Infirmary, to Mr Wardill and his staff at the Newcastle General Hospital for opportunities to study their cases and for the use of their case records, and to my colleagues in the Pathological Department for their autopsy and biopsy reports.

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# THE CLASSIFICATION OF CASES OF GLYCOSURIA<sup>1</sup>

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MEDICAL examination of large sections of the population of military age has provided a better basis for estimating the incidence of glycosuria and for determining the significance of this abnormality than has previously been possible. Several workers have already published data of value in this respect. Thus, Blotner and Hyde (1943 *a*) discovered 33 cases of renal glycosuria, 162 cases of transient glycosuria, and 208 cases of diabetes amongst 45,650 recruits. Peel and Peel (1941) investigated 115 cases of glycosuria and found 43 cases of diabetes, nine border-line diabetics, and 59 cases of renal glycosuria. The present investigation comprised 387 subjects, 382 male and 5 female, found to have glycosuria amongst 40,000 entrants to the services, along with a smaller number of such patients met in ordinary hospital practice. Sugar tolerance tests with 50 gm of glucose were carried out in the fasting state, the venous blood-sugar being determined before ingestion of sugar and at 30 minutes thereafter for two hours. Maclean's method was used throughout for blood-sugar estimation. Samples of urine were obtained on waking, in the fasting state, and two hours after ingestion of sugar. It is particularly important to obtain a sample of urine in the fasting state, since in some cases of renal glycosuria this may be the only sample of urine free from sugar. Urine samples were tested for sugar and acetone and the amount of sugar estimated approximately. Routine inquiry was made as to previous knowledge of glycosuria and diabetic symptoms including polyuria, nocturia, thirst, loss of weight, skin infections, boils, and styes. The material was analysed and classified according to the character of the blood-sugar curve into the following groups

1 Diabetic or prediabetic state	41 cases
2 Border line cases (blood-sugar between 0.15 and 0.19 gm per 100 c c)	112 "
3 Renal glycosuria with normal curve (blood sugar between 0.12 and 0.15 gm per 100 c c)	159 "
4 Renal glycosuria with low curves (blood sugar below 0.12 gm per 100 c c)	52 "
5 Persistent renal glycosuria or renal diabetes	23 "

*Group 1 Diabetes or prediabetic state* This group consisted of 41 men varying in age between 19 and 56 years, of whom 23 were between 30 and 40 years of age and only four in the 18 to 19 years age group. The fasting blood-sugar values varied between 0.062 and 0.363 gm per 100 c c, with

<sup>1</sup> Received April 20, 1946

values below 0.1 gm per 100 c.c. in six, between 0.1 and 0.14 gm per 100 c.c. in 31, and four above 0.14 gm per 100 c.c. At 30 minutes after ingestion of sugar, two showed values below 0.17 gm per 100 c.c., 11 showed values between 0.17 and 0.2 gm per 100 c.c., and 28 showed values above 0.2 gm per 100 c.c. At 60 minutes, values above 0.2 gm per 100 c.c. were found in 13 cases and above 0.15 gm per 100 c.c. in 20, and at two hours, values

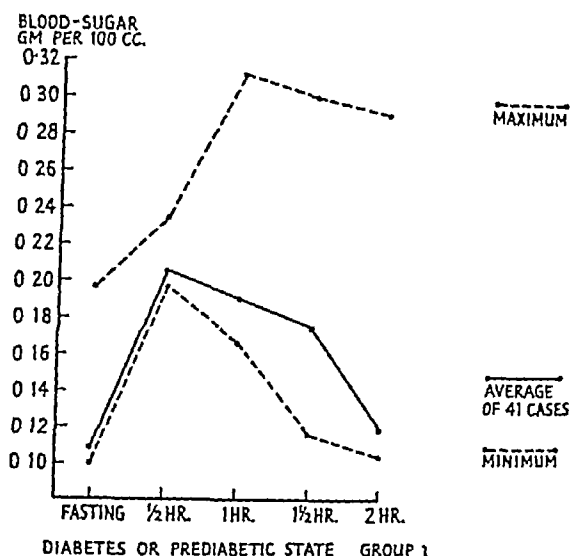


FIG 1

above 0.2 gm per 100 c.c. were present in three cases and above 0.12 gm per 100 c.c. in 16. The highest curve was 0.179, 0.234, 0.312, 0.300, and 0.286 gm per 100 c.c. The average curve from the whole series was 0.109, 0.205, 0.190, 0.175, and 0.119 gm per 100 c.c., shown graphically in Fig 1.

The fasting blood-sugar was above normal in 35 instances in this group. Even slight increase in the fasting blood-sugar was usually found to indicate a diabetic state. The overnight samples of urine were free of sugar in 24 cases, and the fasting urine was free of sugar in all except four instances. The amount of sugar passed after the test was over 3 gm per 100 c.c. in 17 cases and over 2 gm per 100 c.c. in 18, so that the degree of glycosuria was high in the majority, although there was no reduction in the renal threshold for sugar. Acetonuria was found in 11 instances and urobilinogen was in excessive amount in the urine in four cases. Symptoms, including thirst and polyuria or nocturia, were present in 12 instances, while five subjects were overweight. In only one instance was there knowledge of diabetes in the family, where the mother died of diabetes. In two cases blood-sugar curves were repeated within 12 months. In one the curve showed improvement, but was still classed as diabetic, in the second the blood-sugar curve was normal and the urine was free of sugar.

Three cases were later admitted to hospital for treatment of diabetes, one within one week in diabetic ketosis and stabilized on insulin. The second case, a man aged 18 years, was admitted to the Aberdeen Royal Infirmary one year after the diagnosis of diabetes had been made. He had been working in the interval as a trawl fisherman and had taken no precautions with his diet. He had noticed increasing thirst for two months with dryness of the skin, frequency of urination, and rapid loss of weight. The blood-sugar on admission was 0.482 gm per 100 c.c., and intense ketosis was present. There was suppurative otitis media and glossitis. Treatment with insulin and nicotinic acid was commenced and the patient was ultimately stabilized on 28 units of soluble insulin twice daily. The third case, a man of 34 years, showed the following blood-sugar curve on 15.7.40, fasting blood-sugar 0.104, after sugar 0.222, 0.197, and 0.113 gm per 100 c.c. The overnight and fasting samples of urine were free of sugar and the urine contained 2.5 gm per 100 c.c. of sugar after the test. He continued to work as a tramway conductor, and restricted jam and sugar in his diet. He was seen again in June 1945 when he complained of rapid loss of weight, fatigue, thirst, and polyuria. The blood-sugar was 0.48 gm per 100 c.c. and severe ketosis was present. He was stabilized in hospital on 20 units of soluble insulin twice daily.

This group shows the earlier evidences of diabetes, not commonly encountered, at some indefinite period before subjective symptoms and gross clinical signs appear. Occasionally the sugar tolerance test may suggest incipient diabetes, and later observation shows that normal tolerance for sugar has been recovered. Temporary changes in diet or mild sepsis may account for such an occurrence.

*Group 2 Border-line cases* This group consisted of 111 men and one woman found to have glycosuria. The average age was again rather high with 27 below 30 years of age and 65 above 30 years. The average blood-sugar curve for the whole group was 0.093, 0.162, 0.139, 0.117, and 0.098 gm per 100 c.c. In 19 instances the blood-sugar value was over 0.18 gm per 100 c.c. at 30 minutes, and was above 0.16 gm per 100 c.c. at one hour in 30 instances. The blood-sugar value at two hours was still above 0.1 gm per 100 c.c. in 39 instances, in 14 of which the reading was over 0.12 gm per 100 c.c. The fasting blood-sugar values were below 0.1 gm per 100 c.c. in 81 cases and above 0.1 gm per 100 c.c. with a maximum 0.133 gm per 100 c.c. in 31. In the whole group 47 were classed as renal glycosuria, having curves which fell within normal limits and with no symptoms suggestive of diabetes. In 18 a diagnosis of early diabetes was made and in 14 the blood-sugar curve showed delay in assimilation of glucose. The overnight sample of urine contained sugar in 28 patients, with quantities up to 2 gm per 100 c.c. in 10. The fasting samples of urine were free of sugar except for a trace in five cases. Symptoms suggestive of diabetes were common in this group. Frequency of micturition was complained of in 13

instances, thirst in three, and recurrent boils in nine. One patient complained of recent loss of weight and three were obese. There was a curious frequency of association with a history of duodenal ulcer in seven patients, and with the occurrence of intense urobilinuria in six, although only one subject had recently had jaundice. Two had sustained recent head injuries and one patient showed evidences of early thyrotoxicosis. So far as is known to date none of this group has developed frank diabetes. One patient had been seen for glycosuria 11 years previously and was still classed as renal glycosuria. Two pairs of brothers occurred in the group.

*Group 3 Renal glycosuria with normal blood-sugar curves.* This group comprised 158 men and one woman, where the maximum value of the group blood-sugar curve fell between 0.15 and 0.12 gm per 100 c.c. The ages were under 20 in 33 cases, under 30 in 15 cases, under 40 in 74 cases, and above 40 years in four cases. The fasting blood-sugar values all fell below 0.1 gm per 100 c.c. except in four instances, and varied between 0.05 and 0.1 gm per 100 c.c. in 155, with five below 0.06 gm per 100 c.c., 11 below 0.07 gm per 100 c.c., 21 below 0.08 gm per 100 c.c., 36 below 0.09 gm per 100 c.c., and 37 below 0.1 gm per 100 c.c. In 45 the fasting value lay between 0.1 and 0.11 gm per 100 c.c. The average fasting value was 0.089 gm per 100 c.c. The average curve of the group was 0.089, 0.133, 0.119, 0.100, and 0.091 gm per 100 c.c. (Fig. 2). The blood-sugar value returned to below 0.1 gm per 100 c.c. in 81 instances, and below 0.12 mg per 100 c.c. in 61, with 15 above 0.12 gm per 100 c.c., including four above 0.13 and one of 0.15 gm per 100 c.c.

The overnight samples of urine were free from sugar in all except 26 instances where traces of sugar were present, five where 0.5 gm per 100 c.c. of sugar was present, and five where 1 per cent of sugar was present. The fasting samples of urine were free from sugar in all except seven cases included in the above 10, and only one contained more than a trace of sugar. All samples passed after the test contained sugar except in one instance, varying from traces to 37 with 1 per cent of sugar, 13 with 1.5 per cent of sugar, 13 with 2 per cent of sugar, five with 2.5 per cent of sugar, and one with 3 per cent. In nine instances with over 2 per cent of sugar, the overnight and fasting samples had contained sugar. A trace of acetone was found in the urine in the case where most sugar was lost, and one man showed much acetone. He had been treated for six years on a low carbohydrate diet for diabetes. In four instances the men were aware of glycosuria which had been noted on previous medical examinations, and in three cases sugar tolerance tests had been carried out four years earlier with a similar result. In eight instances there was no knowledge of glycosuria having been found on previous examination for entrance to excise, banking, and similar occupations. Certain associated conditions occurred with sufficient frequency to amount to symptom complexes. Excessive amounts of urobilinogen were present in the urine in seven cases, one of whom had been recently under

treatment for hepatitis. Symptoms of duodenal ulcer were present in six instances and two patients had undergone gastro-enterostomy. Two experienced symptoms of hypoglycaemia with blood-sugar values of 0.065 and 0.060 gm per 100 c.c., three were overweight, with one under treatment with thyroid extract. Infections, including boils 7, conjunctivitis 4, urinary 3, various 3, were found or had been recently present. Frequency of micturition, specially at night, was complained of in seven instances, but thirst only once. In six cases there was a definite alcoholic history. The great majority of this group, 120 cases, was classed as uncomplicated renal glycosuria. In four instances no glycosuria was discovered before or after the sugar tolerance test. In four there was delay in return of the blood-sugar to normal with values of 0.133, 0.122, 0.150, and 0.133 gm per 100 c.c. at two hours. These were classed as delayed assimilation or delayed storage of glucose with renal glycosuria. In seven instances there was continuous glycosuria with acetonuria in one case and urobilinuria in another.

*Group 4 Renal glycosuria with low blood-sugar curves.* This group consisted of 50 men and two women where glycosuria was present and where the blood-sugar value did not overstep 0.12 gm per 100 c.c. after ingestion of 50 gm of glucose. Only three were aged over 40 years, and 27 were over 30 years of age. The average blood-sugar curve of the series was 0.081, 0.105, 0.090, 0.089, and 0.075 gm per 100 c.c. (Fig. 2). The fasting blood-sugar values showed 39 below 0.09 gm per 100 c.c., with 11 below 0.07 gm per 100 c.c. The blood-sugar values returned to below 0.09 gm per 100 c.c. in 35 instances, with 16 showing values below 0.07 gm per 100 c.c. The overnight samples of urine contained traces of sugar in 13 instances and 0.5 per cent of sugar in two cases. The fasting samples of urine contained no sugar in all except four instances where traces were present. Samples of urine passed after the test showed traces of sugar in 17 instances, 0.5 per cent in eight instances, 1.0 per cent in five, 1.5 per cent in five, 2 per cent in two, and 2.5 per cent in one case. In 12 instances no sugar was found in any sample, either before or after the sugar tolerance test. In four cases continuous glycosuria was present. In one of these there had been recent rapid loss of weight. Symptoms were few in this group, polyuria was complained of in three cases and boils had been recently present in two cases. Two were of poor physique and fainted during investigation. In one instance the father of the patient had been proved to have renal glycosuria 10 years earlier. All were classed as renal glycosuria.

*Group 5 Renal diabetes.* This group consisted of 21 men and two women (see Table) where the renal threshold for sugar was abnormally low and where sugar was continuously present in the urine. In all cases except two the fasting samples of urine contained sugar. In addition the blood-sugar curves were of the low flat type, the average curve of the series being 0.086, 0.109, 0.100, 0.094, and 0.081 gm per 100 c.c. (Fig. 2). In only four instances did the curve overstep 0.13 gm per 100 c.c., and in 16 instances the maximum



Urine sugar (gm.  
per 100 c.c.)

Blood sugar curve (gm per 100 c.c.)

No	Date	Age	Blood sugar curve (gm per 100 c.c.)					Urine sugar (gm. per 100 c.c.)			Remarks
			Fast- ing	½ hr	1 hr	1½ hr	2 hr	Over- night	Fast- ing	After test	
1	20 9 30	35	0 072	0 117	0 116	0 095	0 095	2 0	2 0	0	Continuous glycosuria in fasting state
2	11 5 40	23	0 062	0 129	—	0 085	0 054	1 0	Trace	0	Urobilinogen + Hypoglycaemic attacks
3	15 11 39	20	0 100	0 090	0 100	0 085	0 085	0 5	0 5	Trace	Mild acidosis No symptoms
4	16 8 40	—	0 102	0 154	0 122	0 100	0 095	1 5	2 0	1 5	No symptoms
5	20 9 40	20	0 085	0 081	0 081	0 062	0 062	1 5	1 5	3 0	Pyuria and frequency viously as diabetic
6	11 3 41	—	0 072	0 104	—	0 077	—	1 5	1 5	3 0	—
7	18 12 39	—	0 085	0 115	0 090	0 087	0 072	—	—	2 0	—
8	16 11 39	21	0 081	0 085	—	0 081	0 077	—	—	2 0	—
9	5 7 40	—	0 085	0 109	0 113	0 095	0 081	2 0	0 5	1 0	—
10	29 11 40	35	0 085	0 109	0 115	—	0 095	Trace	Trace	3 0	Duodenal symptoms and hypoglycaemia
11	21 7 41	39	0 062	0 106	—	0 054	—	Trace	Trace	2 5	Brother has diabetes
12	25 6 41	35	0 090	0 152	0 129	—	0 113	1 0	Trace	1 5	Losing weight No other symptoms
13	16 6 41	38	0 072	0 095	0 095	—	0 085	2 0	1 0	2 0	Polyuria and nocturia Boils
14	2 4 41	20	0 102	0 092	0 062	—	0 058	1 0	1 0	3 0	Mild acidosis Hypoglycaemia Treated as diabetic
15	20 2 41	36	0 077	0 129	0 100	0 067	0 007	1 0	1 0	3 0	No symptoms
16	14 8 41	20	0 083	0 083	0 095	—	—	0 2	Trace	1 0	Duodenal symptoms
17	14 8 41	33	0 100	0 113	0 067	—	—	0 5	0	0 5	Later samples of urine all contained sugar
18	8 5 42	26	0 090	0 117	0 104	0 111	0 058	1 0	0 5	3 0	Giddy attacks Hypoglycaemia
19	28 5 42	18	0 085	0 100	0 111	—	0 100	3 0	2 0	3 0	No symptoms
20	4 10 44	21	0 083	0 122	0 115	0 102	0 095	2 5	2 0	3 0	Enuresis Thirsty Later samples for one year all showed sugar
21	24 7 42	20	0 085	0 077	0 058	—	0 058	0	0	0 5	No symptoms
22	5 1 44	17½	0 092	0 090	0 117	0 095	0 077	2 0	2 0	2 5	No symptoms
23	25 10 44	18	0 087	0 129	0 085	—	0 109	3 0	3 0	2 0	Weakness
24	20 6 44	16	0 106	0 113	0 109	—	0 095	1 0	1 0	2 0	Hypoglycaemia
25	9 2 45	—	0 062	0 077	0 081	—	0 100	1 5	1 0	2 0	Trace
26	2 10 42	22	0 085	0 120	0 038	0 060	0 077	—	—	2 5	Trace
27	7 12 44	—	0 037	0 067	0 048	0 072	0 054	—	—	2 0	Trace

blood-sugar value did not reach 0.12 gm per 100 c.c. The fasting values of the blood-sugar lay within the usual limits of 0.06 and 0.109 gm per 100 c.c., with one exception, and with values below 0.09 gm per 100 c.c. in 16 cases. The blood-sugar returned to values below 0.07 gm per 100 c.c. in six cases at two hours. The amount of sugar lost was large, with over 3 per cent of sugar in the samples of urine passed after the test in seven cases. In several cases repeated samples of urine with water diuresis in the fasting state continued to show sugar. Some of the patients had been completely unaware of any abnormality, while others complained of weakness, lassitude, dizziness, and abdominal discomfort. Four patients showed acetonuria and suffered from symptoms very suggestive of hypoglycaemia. The amount of sugar lost was sufficiently large to produce a state of reversed diabetic metabolism simulating phloridzin diabetes. In three instances the patients had been treated previously for diabetes, the true nature of the cause of glycosuria having escaped detection.

Four cases are described in detail.

**Case 2** The patient was a wireless engineer, aged 23 years, who complained of a feeling of weakness which overtook him occasionally. He had been treated for duodenal ulcer by light diet and Aludrox previously for 10 months. At first this treatment had helped him, but recently his attacks had returned. He had never suffered from thirst, polyuria, or skin sepsis. His weight was unaltered and bowels regular. He was a keen, active man and not anaemic. The pulse-rate was 76 and blood-pressure 130/70. The heart-sounds were normal. There was no evidence on clinical examination of duodenal ulcer or of chronic appendicitis. The mouth and throat were clean and reflexes normal. A fractional test-meal showed moderate hyperacidity of the fasting stomach contents, but normal acidity in response to the meal. No occult blood was present in the stomach contents. A sugar tolerance test gave the following blood-sugar curve, fasting 0.062, with later values of 0.129, 0.085, and 0.054 gm per 100 c.c. The overnight sample of urine contained sugar and urobilinogen but no acetone, the fasting sample of urine contained a trace of sugar and the sample passed after the test contained 3 per cent of sugar. The patient had symptoms of hypoglycaemia towards the end of the sugar tolerance test, becoming pale and dizzy with cold perspiration. He said that this was the type of attack of which he complained. This man

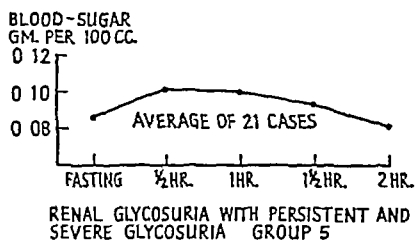
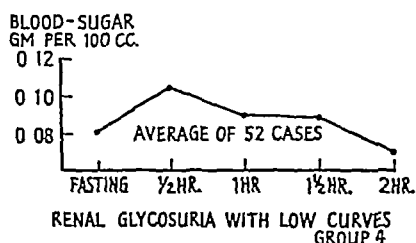
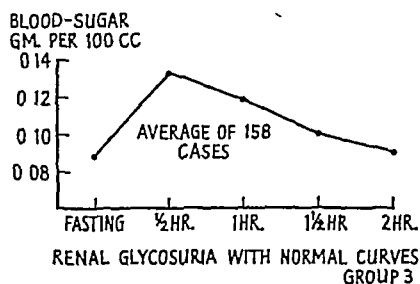


FIG 2

## Renal Diabetes

No	Date	Age	Blood sugar curve (gm per 100 c c)					Urine sugar (gm. per 100 c c)		Remarks		
			Fast- ing	½ hr	1 hr	1½ hr.	2 hr	Over- night	Fast- ing		After test	
1	20 9 30	35	0 072	0 117	0 146	0 095	0 095	2 0	2 0	2 0	0	Continuous glycosuria in fasting state Urobilinogen + Hypoglycaemic at- tacks
2	11 5 40	23	0 062	0 120	—	0 085	0 054	1 0	Traco	3 0	0	
3	15 11 39	20	0 100	0 090	0 100	0 085	0 085	0 5	0 5	3 0	Trace	
4	16 8 40	—	0 102	0 154	0 122	0 100	0 005	1 5	2 0	1 5	0	
5	20 9 40	20	0 085	0 081	0 081	0 002	0 062	1 5	1 5	3 0	0	
6	11 3 41	—	0 072	0 104	—	0 077	—	1 5	1 5	3 0	0	No symptoms
7	8 4 38	—	0 085	0 115	0 090	0 087	0 072	—	—	2 0	0	Pyuria and frequency Treated pro- vously as diabetic
8	18 12 39	—	0 081	0 085	—	0 081	0 077	—	—	2 0	Trace	—
9	16 11 39	21	0 085	0 100	0 113	0 095	0 081	2 0	0 5	1 0	0	—
10	5 7 40	—	0 133	0 141	0 109	—	0 095	Traco	3 0	2 5	0	—
11	29 11 40	35	0 085	0 109	0 115	—	0 077	Traco	Traco	3 0	+	—
12	21 7 41	39	0 062	0 109	—	0 054	—	Traco	Traco	2 5	0	—
13	25 6 41	35	0 090	0 152	0 120	—	0 113	1 0	Traco	1 5	0	Duodenal symptoms and hypoglycaemia Brother has diabetes
14	16 6 41	38	0 072	0 095	0 095	—	0 085	2 0	1 0	2 0	0	Losing weight No other symptoms
15	2 4 41	20	0 102	0 092	0 062	—	0 058	1 0	1 0	3 0	0	Polyuria and nocturia Boils
16	20 2 41	36	0 077	0 129	0 100	0 067	0 067	1 0	1 0	3 0	Trace	—
17	14 8 41	20	0 083	0 083	0 095	—	—	0 2	Traco	1 0	0	Mild acidosis Hypoglycaemia Treated as diabetic
18	14 8 41	33	0 109	0 113	0 067	—	—	0 5	0	0 5	0	No symptoms
19	8 5 42	26	0 090	0 117	0 104	0 111	0 058	1 0	0 5	3 0	Trace	Duodenal symptoms
20	28 5 42	18	0 085	0 100	0 111	—	0 100	3 0	2 0	3 0	Trace	Later samples of urine all contained sugar
21	4 10 44	21	0 083	0 122	0 115	0 102	0 095	2 5	2 0	3 0	Trace	Giddy attacks Hypoglycaemia
22	24 7 42	20	0 085	0 077	0 058	—	0 058	0	0	0 5	0	—
23	5 1 44	17½	0 092	0 090	0 117	0 095	0 077	2 0	2 0	2 5	0	No symptoms
24	25 10 44	18	0 087	0 129	0 085	—	0 100	3 0	3 0	2 0	0	Enuresis Thirsty Later samples for one year all showed sugar
25	20 6 44	16	0 106	0 113	0 109	—	0 085	1 0	1 0	2 5	0	No symptoms
26	9 2 45	—	0 062	0 077	0 081	—	0 100	1 5	1 0	2 0	0	Weakness
27	2 10 42	22	0 085	0 129	0 038	0 080	0 077	—	—	2 5	Trace	—
28	7 12 44	—	0 037	0 067	0 048	0 072	0 054	—	—	2 0	Trace	Hypoglycaemia

Continuous glycosuria in fasting state  
Urobilinogen + Hypoglycaemic at-  
tacksMild acidosis No symptoms  
No symptomsPyuria and frequency Treated pre-  
viously as diabeticDuodenal symptoms and hypoglycae-  
mia Brother has diabetes  
Losing weight No other symptoms  
Polyuria and nocturia BoilsMild acidosis Hypoglycaemia Treated  
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sugar

Giddy attacks Hypoglycaemia

No symptoms

Enuresis Thirsty Later samples for  
one year all showed sugarNo symptoms  
Weakness

Hypoglycaemia

0.067, 0.048, 0.072, and 0.054 gm per 100 cc with sugar present in all samples of urine. On 21.5.45 as an out-patient, the urine still contained sugar with a blood-sugar value of 0.085 gm per 100 cc.

### *Discussion*

Reference in the literature to this type of disturbance of carbohydrate metabolism is scanty. Wilder (1940) quoted a case of renal glycosuria where sugar was passed in the urine in the fasting state with a blood-sugar value of 0.092 gm per 100 cc and after a sugar tolerance test with blood-sugar returning to 0.070 gm per 100 cc, and pointed out that renal dextrosuria may result in hypoglycaemia when the renal threshold is greatly depressed. He mentioned a case where the renal threshold was so low that 60 gm of glucose was lost in the urine daily on a diet containing 100 gm of carbohydrate, and ketonuria was also present. Macpherson (1941) described a case of renal glycosuria with hypoglycaemia in a soldier, where the blood-sugar curve was 0.08, 0.14, 0.06, 0.052, and 0.08 gm per 100 cc. An attack of hypoglycaemia occurred during the test. Patterson (1925) described a similar case where ketonuria was also present.

The present series indicates that the incidence of this condition is greater than records in the literature would suggest. The pathogenesis remains obscure, but if it be assumed that abnormally low values of the renal threshold are primary, then hyperinsulinism may be compensatory to depress the blood-sugar and limit the degree of glycosuria. The duration of this type of glycosuria is not temporary since sugar tolerance tests were repeated in four cases of the series with similar results at intervals up to four years. The type of sugar passed has not been identified in the series, but has always been increased in amount on ingestion of glucose. Glucosazone was easily formed from the sugar passed in the fasting state in Case 22. Analysis of the whole group shows that the incidence of glycosuria in the male population between the ages of 18 and 40 years approaches one per cent, a figure which compares closely with 0.8 per cent found by Blotner and Hyde (1943*b*). Of such cases of glycosuria discovered accidentally, about 10 per cent are diabetics, mostly in the early stages of the disease, and 90 per cent are cases of renal glycosuria. Earlier investigations did not indicate that renal glycosuria was so common. There are two possible reasons for this anomaly. The figures for earlier series, such as those of Joslin, Root, White, and Marble (1940) who found 44 cases in 13,000 glycosurics, Fitz (1931) who found 36 cases in 10 years, Marble, Joslin, Dublin, and Marks (1939), and Fowler (1933), were mostly drawn from patients already in hospital. As most patients with renal glycosuria are without symptoms, they are not admitted to hospital in the ordinary course. Also the criteria for the diagnosis of renal glycosuria vary with different workers. If this diagnosis be limited to glycosuria at fasting levels of the blood-sugar, as suggested by Marble, Joslin, Dublin, and Marks (1939) and Joslin, Root, White, and Marble (1940), then the condition is rare, but if glycosuria at

was observed later at Manchester Royal Infirmary where these findings were confirmed. Sugar was found in the urine at each attendance at a follow-up clinic and the blood-sugar values two hours after food lay between 0.086 and 0.095 gm per 100 c.c. I am indebted to Dr A. G. Hepplestone for the note on the further record of the case.

Case 5, a man aged 20 years. Admitted to Woodend Hospital 12.37 with pneumonia. He recovered completely by crisis in five days but was found to have sugar in the urine (0.7 gm per 100 c.c.). A blood-sugar curve on 12.2.37 gave 0.06, 0.087, 0.081, 0.066, and 0.062 gm per 100 c.c. Much sugar was present in all specimens of urine. He was discharged on 3.3.37 and with a diagnosis of renal glycosuria. On 19.9.40 he was referred to hospital by his doctor who had found sugar in his urine, confirming a finding made by a Royal Air Force medical board. A sugar tolerance test at this time gave 0.085, 0.081, 0.081, 0.062, and 0.062 gm per 100 c.c., with 1.5 per cent of sugar in the fasting sample of urine and 3 per cent in the sample passed after the test. He said that he knew that he had had diabetes for three years, but had taken an ordinary diet except for sugar in tea. He ate sweets and biscuits as obtainable. In addition the urine contained pus, and right-sided pyelitis was diagnosed, for which he was later treated. On 11.3.41 he again presented himself for medical examination. The blood-sugar curve gave 0.072, 0.104, and 0.077 gm per 100 c.c. and all samples of urine contained much sugar. The urine deposit then contained only a few pus cells.

Case 22, a girl aged 16 years. The patient complained in June 1944 of attacks of pain in the right lumbar region. Full clinical examination revealed no abnormality. A pyelogram was normal. Sugar was present in the urine and a sugar tolerance test on 20.6.44 gave a low curve, 0.106, 0.113, 0.109, and 0.095 gm per 100 c.c. The overnight and fasting samples of urine contained 1 gm per 100 c.c. of sugar and a sample of urine passed after the test showed 2.5 gm per 100 c.c. of sugar. In January 1945 laparotomy was performed and the abdomen was found to contain a small amount of free fluid and inflamed mesenteric glands. The appendix was normal but was removed. The patient made a poor recovery and a slow convalescence and did not feel fit to work. Sugar was continually present in the urine. At a later period of hospital observation, daily samples of urine were collected on a diet of 2,100 calories with 150 gm of carbohydrate. For a period of 10 days the urine volume lay between 28 and 44 oz with from 1.0 to 1.5 gm per 100 c.c. of sugar and a total loss of 15 to 17 gm of glucose daily. The sugar tolerance test now gave a very low curve, 0.062, 0.077, 0.081, and 0.100 gm per 100 c.c. In the fasting state, water was given to drink and hourly samples of urine collected. Sugar was present in all samples, although the urea content fell progressively over four hours from 2.2 to 0.3 gm per 100 c.c. Glucosazone was formed from the sugar in the urine.

Case 23, a man aged 22 years. The patient complained of headaches, thirst, polyuria, and nervousness for two years. Nocturia had been troublesome at times, with enuresis occasionally. He had lost weight and suffered from giddy attacks. He had been discharged from the army and was said to have diabetes. A sugar tolerance test on 2.10.42 gave 0.085, 0.129, 0.060, and 0.077 gm per 100 c.c. All samples of urine contained sugar, and acetone was frequently present. The patient was admitted to the Aberdeen Royal Infirmary on 7.12.44 complaining of persistent attacks of dizziness during the night and also of polyuria. A tolerance test at this time showed 0.037,

0.067, 0.048, 0.072, and 0.054 gm per 100 c c with sugar present in all samples of urine. On 21.5.45 as an out-patient, the urine still contained sugar with a blood-sugar value of 0.085 gm per 100 c c.

### *Discussion*

Reference in the literature to this type of disturbance of carbohydrate metabolism is scanty. Wilder (1940) quoted a case of renal glycosuria where sugar was passed in the urine in the fasting state with a blood-sugar value of 0.092 gm per 100 c c and after a sugar tolerance test with blood-sugar returning to 0.070 gm per 100 c c, and pointed out that renal dextrosuria may result in hypoglycaemia when the renal threshold is greatly depressed. He mentioned a case where the renal threshold was so low that 60 gm of glucose was lost in the urine daily on a diet containing 100 gm of carbohydrate, and ketonuria was also present. Macpherson (1941) described a case of renal glycosuria with hypoglycaemia in a soldier, where the blood-sugar curve was 0.08, 0.14, 0.06, 0.052, and 0.08 gm per 100 c c. An attack of hypoglycaemia occurred during the test. Patterson (1925) described a similar case where ketonuria was also present.

The present series indicates that the incidence of this condition is greater than records in the literature would suggest. The pathogenesis remains obscure, but if it be assumed that abnormally low values of the renal threshold are primary, then hyperinsulinism may be compensatory to depress the blood-sugar and limit the degree of glycosuria. The duration of this type of glycosuria is not temporary since sugar tolerance tests were repeated in four cases of the series with similar results at intervals up to four years. The type of sugar passed has not been identified in the series, but has always been increased in amount on ingestion of glucose. Glucosazone was easily formed from the sugar passed in the fasting state in Case 22. Analysis of the whole group shows that the incidence of glycosuria in the male population between the ages of 18 and 40 years approaches one per cent, a figure which compares closely with 0.8 per cent found by Blotner and Hyde (1943b). Of such cases of glycosuria discovered accidentally, about 10 per cent are diabetics, mostly in the early stages of the disease, and 90 per cent are cases of renal glycosuria. Earlier investigations did not indicate that renal glycosuria was so common. There are two possible reasons for this anomaly. The figures for earlier series, such as those of Joslin, Root, White, and Marble (1940) who found 44 cases in 13,000 glycosurics, Fitz (1931) who found 36 cases in 10 years, Marble, Joslin, Dublin, and Marks (1939), and Fowler (1933), were mostly drawn from patients already in hospital. As most patients with renal glycosuria are without symptoms, they are not admitted to hospital in the ordinary course. Also the criteria for the diagnosis of renal glycosuria vary with different workers. If this diagnosis be limited to glycosuria at fasting levels of the blood-sugar, as suggested by Marble, Joslin, Dublin, and Marks (1939) and Joslin, Root, White, and Marble (1940), then the condition is rare, but if glycosuria at

any level of the blood-sugar below 0.15 gm per 100 c.c. be classed as renal, then this abnormality is relatively common in the general male population, although it seems to be uncommon amongst women. Recognition of general manifestations of mild hypoglycaemia of this type derives from other sources. Thus, Alexander and Portis (1944) made a study of hypoglycaemia as the basis of the neurotic symptom of fatigue. Glucose tolerance tests showed flat curves in the majority of cases, although the basal blood-sugar was not below the normal limits. They postulated a type of vagal hyperinsulinism in these cases. There is at present no clear explanation of the pathogenesis of renal glycosuria. Some workers, such as Mirsky and Nelson (1943), state that the rate of glomerular filtration exceeds that of tubular reabsorption for glucose in renal glycosuria and either or both may be abnormal, but, as shown by Friedman, Selzer, Sugarman, and Sokolow (1942), the effective renal blood flow, glomerular filtration, and filtration fraction are within normal limits in moderate renal glycosuria. In addition, their observations indicated that at higher levels of blood-sugar, tubular reabsorption of glucose was better than in normal persons, although reabsorption at low levels of the blood-sugar was impaired. In any case it is generally agreed that the renal threshold for sugar may vary in otherwise normal persons between the levels of 0.18 gm per 100 c.c. and low fasting levels. In view of the fact that those with very low levels may continually lose much sugar by this means and many develop symptoms attributable to this abnormality, a differentiation should be made between this syndrome and simple renal glycosuria. The term renal diabetes, which in fact describes the syndrome, seems suitable for this purpose.

### Summary

In 387 cases of incidental glycosuria, 41 were classified as diabetes or in the prediabetic state, 112 as doubtfully diabetic, 159 as renal glycosuria with blood-sugar curves rising to 0.15 gm per 100 c.c., 52 as renal glycosuria with blood-sugar curves up to 0.12 gm per 100 c.c., and 23 as renal glycosuria with low values of the blood-sugar and persistent glycosuria even at fasting levels of the blood-sugar. The last group is considered in detail and it is suggested that the term renal diabetes should be used for this syndrome.

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CLINICAL ASPECTS OF POLYARTERITIS NODOSA<sup>1</sup>

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(From the Medical Division of Princess Mary's  
Royal Air Force Hospital, Halton)*Introduction*

SINCE the clinical and pathological definition of polyarteritis (peri-arteritis) nodosa by Kussmaul and Maier in 1866, and the formulation 12 years later of Meyer's (1878) diagnostic triad of chlorotic marasmus, polymyositis and polyneuritis, and gastro-intestinal symptoms, more than 400 cases have been recorded. Nearly 200 of these appear in the English and American literature. Nevertheless, polyarteritis nodosa is still more often diagnosed at autopsy than during life, and although the proportion of cases recognized *ante mortem* in the more recently recorded material is substantially higher than the 12 per cent estimated by Spiegel in 1936, cases are often missed even in the largest hospitals and by the most experienced physicians. This entails not only a loss of valuable clinical and pathological information, but also the sterilization of such therapeutic endeavour as is suggested by recent work on the aetiology of the condition. We believe that this difficulty is only in part inherent in the behaviour of the disease, and that in many cases it is due either to failure to consider the diagnosis in a difficult case, or to rejection of the diagnosis, once considered, because of the absence of one or more signs, such as subcutaneous nodules or eosinophilia, which are considered typical, but are actually of infrequent occurrence. The present paper is an attempt to clarify the clinical picture of polyarteritis nodosa with reference to the more important literature and to diagnostic difficulties recorded and personally encountered.

*Aetiology*

It has long been recognized clinically that polyarteritis nodosa may follow specific bacterial infections. The role of streptococcal infection was stressed by many of the earlier writers, while tonsillitis (Vining, 1938), sinusitis (Boyd and Nussbaum, 1936), erysipelas (Dietrich, 1933), scarlet fever with or without glomerulonephritis (Manges and Baehr, 1921, Ophüls, 1923, Spiegel, 1936, Selye and Pentz, 1943), infected wounds (Lindberg, 1933), and gonococcal (Helpern and Trubek, 1933) and meningococcal (Spiegel, 1936) infections have all preceded polyarteritis in recorded cases. There is some evidence that trichiniasis (Reimann, Price, and Herbut, 1943), tuberculosis (Trasoff and Scarf, 1940, Reyna and Cardeza, 1943), and syphilis (Chvostek

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and Weichselbaum, 1877, Klotz, 1917, Gruber, 1926, Gray, 1932, Volland, 1935) may occasionally stand in a similar relationship to the condition, while throughout the recorded material one cannot fail to be impressed by the frequency with which non-specific minor respiratory infections were antecedent to the illness

The not infrequent finding, in cases reported early in the century, of evidence of streptococcal infection either during life or on bacteriological examination of autopsy tissues, led to a suspicion that this organism stood in some specific relation to polyarteritis nodosa. Frequent clinical and pathological failure to demonstrate streptococci, however, militated against the general acceptance of this idea, which gave place to the tacit assumption that the causal organism was an unidentified ultramicroscopic virus. There was no positive evidence in favour of this view, and it ignored the frequency of the various antecedent bacterial infections so often observed in relation to the disease. Experimental attempts to reproduce the disease (von Haun, 1920, Harris and Friedrichs, 1922) had in common their dependence on repeated injection of foreign tissue extracts into experimental animals, and the absence of satisfying confirmation of claimed results by subsequent experimenters.

A more hopeful line of approach was suggested by the observation that polyarteritis had followed serum sickness after the administration of anti-pneumococcal serum (Clark and Kaplan, 1937) and had also ensued after allergic manifestations provoked by non-bacterial antigens (Ehrström, 1938). These observations, the general relationship of acute and subacute rheumatism to polyarteritis, and the finding of Aschoff bodies at autopsy in this condition (Rothstein and Welt, 1933, Friedberg and Gross, 1934, Spiegel, 1936), indicated the possibility that the development of polyarteritis might be related to allergy-immunity mechanisms rather than to the preceding infection itself. Other clinical observations have shown that positive evidence of a past or family history of allergic phenomena is found in 15 per cent (Harris, Lynch, and O'Hare, 1939) and of asthma in 18 per cent of cases (Wilson and Alexander, 1945). Certainly asthma, pruritus, urticaria, angio-neurotic oedema, glomerulonephritis, and other symptoms commonly considered to be related to hypersensitive states are found as clinical features of an appreciable proportion of developed cases. Recent clinical and experimental observations (Gruber, 1926, Swift, Derick, and Hitchcock, 1928, Masugi and Sato, 1934, Ehrström, 1938) have related polyarteritis nodosa to other allergic phenomena, and the studies of Cohen, Khne, and Young (1936) have shown the histological similarity of the vascular lesions of polyarteritis to the milder and essentially reversible changes found in the histamine-reaction and the allergic wheal. In particular the clinical and experimental studies of Rich (1942) and Rich and Gregory (1943) have clarified this relationship. These latter workers found lesions of polyarteritis nodosa in patients dying after serum sickness and also after manifestations of hypersensitivity to sulphonamides, and demonstrated the experimental

production of polyarteritis nodosa, sometimes accompanied by glomerulonephritis, in rabbits after the establishment of an anaphylactic state, analogous to human serum sickness, by the repeated injection of foreign serum. This work clearly establishes that some cases of polyarteritis represent non-specific manifestations of anaphylactic hypersensitivity to various antigens, a possibility suggested 20 years ago by Gruber (1925). It seems likely that the responsible antigen is usually bacterial in origin, but further cases have been reported, apparently related to hypersensitivity to sulphonamides (Rosenak and Maschmeyer, 1945), while desoxycorticosterone acetate (Selye, Beland, and Sylvester, 1944), thiourea (Gibson and Quinlan, 1945), organic arsenicals (Miller and Nelson, 1945), and iodine (Rich, 1945) have also come under suspicion as possible aetiological agents. The search for a possible antigen and for familial or personal evidence of an allergic history is thus an important feature in the diagnosis of a suspected case. Controlled intradermal testing with suspected antigens may prove useful, though in the few cases of which we have had personal experience it has yielded disappointing results. The therapeutic importance of an attempt to identify and eliminate the suspected antigen is evident, and when it cannot be identified, but is suspected to be of bacterial origin, the administration of antibiotics is rational and might be expected to produce occasional results in cases where the changes are not already irreversible. Improvement (Foster and Malamud, 1941) and recovery (Goldman, Dickens, and Schenker, 1942) have already been recorded in some cases after the administration of sulphonamides, though in none of these cases was the preceding aetiological agent clearly identified.

### *Pathology*

The morbid anatomy of the condition is well described by Gruber (1925) and Arkin (1930). For clinical purposes it is enough to say that polyarteritis nodosa represents a destructive 'inflammatory-necrotizing' reaction of the vascular tree, in which the small elastic arteries and arterioles, such as those of the heart, skeletal musculature, and mesentery, are chiefly affected, and with a tendency to healing by granulation, scarring, and occasional aneurysm formation. Peri-arteritis is a misnomer, the lesion is essentially a necrotizing panarteritis with fibrinoid necrosis, affecting all coats of the artery, but initially the inner media and subintima, and with peri-arteritis as a secondary phenomenon. The lesions occur in crops. They are found along the length of the vessel, and on section often involve only a segment of the arterial circumference, hence the necessity for serial sections of biopsy material if the not infrequent error of discarding the diagnosis on the strength of one biopsy section showing a healthy vessel wall is to be avoided. There is fibrinoid exudation with consequent swelling of the vessel wall, separation of the internal elastic lamina, infiltration with inflammatory cells, obliteration of the lumen by mural swelling, and frequently thrombosis and recanalization. The weakened and necrotic wall granulates, becomes scarred, and may yield,

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intervals. The number of nodules and the total area of discoloured skin have waxed and waned. His general condition is much improved in the summer, when he gains weight and is able to do half a day's work. On one occasion he was found to have a mild lower motor neurone seventh nerve weakness, and later an area of bluish skin over the dorsum of the first right metatarsal bone was found to be anaesthetic to pin prick and light touch. When last seen in February 1946, his clinical condition was little changed, but the total white-cell count had risen to 24,000 per c mm with 85 per cent polymorphonuclear cells, and the erythrocyte sedimentation rate was 86 mm in one hour. A 30 gm course of sulphapyridine and 4,000,000 units of penicillin administered over a period of eight days failed to alter the clinical course of the disease.

*Case 2. A syndrome of benign recurrent peripheral thromboses with subcutaneous nodules, but without serious systemic upset or any evidence of visceral involvement, showing the histological picture of acute arteritis and peri-arteritis on muscle biopsy.*

A 40-year-old officer, with no significant past or family history, except that his mother had had a leg amputated in late life for some vascular disorder, had a total dental extraction in October 1939, after which he felt unwell, and in November had a few days acute pain in the right testicle which cleared up. In June 1940, he was seized with acute pain in the right calf accompanied by swelling of the calf muscles and the ankle. Fourteen days later this was followed by a recurrence of acute pain in the right testicle persisting for about a week. Within a month of the onset the symptoms had cleared and he returned to work. In September 1940, he had a recurrence of similar symptoms affecting the right leg, in association with a carbuncle in the left axilla. As in the previous attack, he had no fever, but during this second episode he developed painful, tender spots on the anterior aspect of the medial epicondyle of the left elbow and over the ramus of the right mandible. There were also aching pains in the right ankle and knee-joint. After six weeks of rest he recovered completely and returned to work. In January 1941, he had a further attack of right testicular pain accompanied by severe aching pains in the right leg and in both arms. He developed tender nodules in the muscles of the right calf, and a diagnosis of thrombophlebitis migrans was made. Full hospital investigations revealed no significant findings, blood counts, X-rays of chest, sinuses and teeth, blood Wassermann and gonococcal complement fixation tests, blood-pressure, urine, and erythrocyte sedimentation rate were all normal, and he recovered within five weeks. Except for recurrent furunculosis in September and October 1942, he was well until August 1943, when he developed pain, swelling, and redness in the right ankle, spreading up the right calf and associated with an area of sensory loss over the heel. On this occasion he showed a more marked constitutional disturbance, with a sore throat and widespread enlargement of lymphnodes, and was readmitted to hospital. Over both legs he showed patchy areas of dusky, hard, inflammatory swelling varying from a half to one and a half inches in diameter, some apparently in relation to superficial veins, others deep and nodular. Suspicions of erythema nodosum were discarded when he developed several small, subcutaneous, non-tender nodules in the forearms. These showed no discoloration and no evident inflammatory reaction. Biopsy of a small nodule on the anterior aspect of the left leg showed that it was in fact related to a small artery and not to a vein, and the appearances of this vessel with mural oedema, fibrinoid necrosis,

forming multiple small aneurysms. These aneurysms may present as palpable subcutaneous nodules which have been recorded in not more than 16 per cent. of cases (Harris, Lynch, and O'Hare, 1939), and are usually filled with organizing thrombus, although occasionally pulsatile. Similar nodules are an occasional clinical finding in cases without pathological aneurysm formation, when they may result simply from marked local swelling of the vessel wall with foci of perivascular oedema and cellular infiltration (Spalding, 1940), or from similar foci sometimes found independent of blood vessels (van Bogaert, Stolz, and Ley, 1932). Despite some histological objections, summarized by Vining (1938), there is much evidence to suggest that the arterial changes of polyarteritis nodosa differ only in degree from the less severe acute arteritis with mural cellular infiltration which is seen in acute rheumatism (von Glahn and Pappenheimer, 1926, Shaw, 1929, Fraser, 1934). Indeed, such minimal changes may be found as the only manifestations of polyarteritis in mild cases, or in the less severely involved vessels of florid cases. Perhaps the most remarkable feature of the condition is that the vascular changes may on occasion be limited almost entirely to the vessels of one system or to a few isolated organs, with the result that no single clinical finding is invariably present. Not only fever and leucocytosis, but even blood and albumin in the urine, may be absent throughout prolonged periods of observation. In cases with neurological signs particularly, there may be no clinical evidence and only scanty histological evidence that other tissues are involved (Kernohan and Woltman, 1938). Two of our own histologically verified cases are remarkable for their chronic course and for the absence of any evidence of gross visceral involvement during several years' observation.

*Case 1 Recurrent subcutaneous nodules and skin manifestations in a boy of 14 years with symptoms persisting after five years' observation*

A boy of 14 years was first admitted to hospital in December 1941. He complained of the presence of crops of painful nodules over both shoulders and of a dull aching pain in both knees during the previous week. In view of his temperature of 102° F, pulse rate of 100, and an apical systolic murmur, he was diagnosed as a case of rheumatic fever. During the next few months his temperature and pulse rate gradually subsided, although they were apparently uninfluenced by salicylates, and he continued to develop fresh crops of nodules over the trunk and limbs every two or three weeks. The lesions were small and there was no discoloration or tenderness. After seven months he was transferred to a convalescent home, only to be readmitted in November 1942, when examination revealed multiple, diffuse, bluish-purple areas of skin discoloration on his trunk and the flexor surfaces of the limbs. The nodules were more profuse than previously, many showed a bluish discoloration and were tender, and they were scattered over all areas of the body except the head and neck. He was then afebrile, with a normal pulse-rate and normal heart sounds. His blood-pressure was 125/90, and all relevant investigations were negative. Early in 1943 a nodule from the left calf was removed and showed the histological changes of acute arteritis and peri-arteritis nodosa. During the past two years he has been seen at frequent

in recovered cases 12 months after diagnosis by biopsy That it may be clinically so is demonstrated by the case of von Haun (1920) returned to full military service after an authenticated illness Scrutiny of the recovered cases in the literature indicates the apparent infrequency of residual disability Alkiewicz (1933) recorded a patient surviving and healthy 25 years after recovery

The widespread nature of the pathological changes is reflected in symptoms so variable, scattered, and superficially unrelated that no standard clinical description can do justice to the polymorphic nature of the illness There are, however, some features which, if not universal, are so frequent that in their absence a clinical diagnosis of polyarteritis should be entertained with reluctance Fever probably occurs at some time during the course of the disease in every case, being observed in 80 per cent of those recorded by Harris, Lynch, and O'Hare (1939), though there may be prolonged afebrile periods even when the condition is progressive More than half the cases have an acute onset and this is usually febrile When fever does occur it may be low and irregular, but quite often it is high, prolonged, and altogether more severe than can be accounted for by the findings on clinical examination Tachycardia is usually pronounced and often more marked than would be expected from the degree of fever Polymorphonuclear leucocytosis, often reaching high figures, is found in the large majority of cases, 70 per cent according to Harris, Lynch, and O'Hare (1939), and it is observed at times even in the absence of fever, whilst an increased count or a shift to the left may be associated with complications or an extension of the disease More rarely leucopenia (Matras, 1938) or a marked relative lymphocytosis has been recorded (Motley, 1936, Spiegel, 1936, Grant, 1939), and in one of Spiegel's cases it led to a mistaken diagnosis of monocytic leukaemia The erythrocyte sedimentation rate has been constantly raised in cases where it was recorded, and this is probably related to a lowered serum protein with reversal of the albumin globulin ratio Clinically these general signs of an infective process are puzzling because in the majority of cases no significant infective focus can be found, despite exhaustive clinical investigations, and many cases of polyarteritis nodosa are labelled 'pyrexia of unknown origin' for prolonged periods Since Datnowski (1909) described eosinophilia in the condition it has been accepted as a typical feature, but although high figures have been recorded (79 per cent of 32,000 white blood cells (Strong, 1928)) 84 per cent (Wilson and Alexander, 1945)), it is in fact a rare finding, occurring in less than 20 per cent of cases (Middleton and McCarter, 1935, Harris, Lynch, and O'Hare, 1939) and usually with antecedent or coincident asthma In our own experience eosinophilia may be found in only one of many serial blood examinations A moderate anaemia of orthochromic or hypochromic type, with red-cell counts falling as low as 3,000,000 per c mm in long-standing cases, is found in about half the recorded material

Pathologically the kidneys are the organs most frequently involved, showing lesions at autopsy in 87 per cent of cases (Harris, Lynch, and



cellular infiltration, with polymorphs, lymphocytes and eosinophils, peri-arterial infiltration and small haemorrhages, were considered typical of an acute arteritis and peri-arteritis of polyarteritis nodosa type. Again he recovered, and returned to duty in October. He remained well until October 1945, but since this time has had three further minor attacks of pain and swelling, on these occasions in the left calf, and in one of these attacks there was also severe pain in the left elbow-joint, and a subcutaneous nodule on the abdominal wall. There is still no evidence of visceral involvement, and his general condition remains good.

In general, the symptomatology can be deduced from the usually widespread pathological involvement of the vascular system. The characteristic, though rarely seen, subcutaneous nodules represent the actual lesion in the artery, most of the other symptoms are secondary results of tissue ischaemia, and are protean in nature, depending on the accident of situation. The third category of symptoms, comprising skin eruptions and necroses, which are particularly evident in some childhood cases, myocardial Aschoff nodes, verrucose endocardial vegetations, and possibly some varieties of polyneuritis, may be toxic in nature.

#### *The Natural History of the Disease and its General Features*

Polyarteritis nodosa may occur at any age, and three months and 78 years represent the recorded extremes. Males predominate in a ratio of at least three to one, and the maximum incidence is in the third decade. The duration of the condition varies from a few days (Fishberg, 1923) or even a few hours (Thinnes, 1924) to several years. Recurrent symptoms over periods of four (Jäger, 1933) to 14 years (Heinrich, 1937) have been recorded on half a dozen occasions, though the average length of the illness is from six to 12 months.

The chief reviews in English of the clinical literature of polyarteritis nodosa are those of Lamb (1914), Strong (1928), Curtis and Coffey (1934), and Harris, Lynch, and O'Hare (1939). Many of the earlier cases are inadequately reported, while changed orientations have led to changed accentuation even in the elicitation of clinical histories, as for instance in the role of allergic factors, and only the last of these reviews, dealing with 101 cases recorded in the English literature with 87 autopsies, is of much value as indicating the approximate numerical frequency of clinical features and prognosis. In this latter direction the figures have been unduly weighted by the number of reported cases coming to autopsy, and it is noteworthy that although the disease was at first considered invariably fatal, the percentage estimate of recovery has risen steadily since Benedict (1907) reported the first recovery, from Lamb's (1914) five per cent. to Grant's (1939) observation that of 50 cases recognized during life, half recovered. In view of the difficulties of diagnosis this is almost certainly an underestimate of the actual recovery rate. That recovery may be pathologically complete is shown by the observations of Reimann, Price, and Herbut (1943) and Erlandsson (1931) who demonstrated the absence of lesions at autopsy.

for the previous four months. He had a past history of gonorrhoea at the age of 22 years and of the common illnesses of childhood. He was of good physique and had no abnormal physical signs in the heart or chest, and a normal blood-pressure. There was diffuse epigastric tenderness, several localized tender areas in both glutei medii and calves, and pain in the lumbar region and down the legs on straight leg raising. The right knee-jerk and both ankle-jerks were absent and there was bilateral patchy hypalgesia of stocking distribution. The plantar reflexes were flexor and the remainder of the central nervous system showed no abnormal findings. He had a haemoglobin of 80 per cent and a leucocytosis of 14,000 cells per c mm, predominantly polymorphonuclear cells, but with 5 per cent of eosinophil cells. His erythrocyte sedimentation rate was 50 mm in one hour, and his urine showed a trace of albumin, a few granular casts, and a moderate number of red blood cells and pus cells. All other investigations, including X-ray studies of the spine, barium meal and barium enema examinations, and examination of cerebrospinal fluid, were negative. He remained in hospital for six weeks, maintaining an irregular fever reaching a maximum of 100.5° F in the evenings, before he had a large melaena which reduced his haemoglobin to 53 per cent. After recovering from this a further barium meal was again normal, but in view of the combination of fever, polyneuritis and continuing abdominal pain, a muscle biopsy was performed on the right calf, and serial sections showed the typical changes of subacute polyarteritis nodosa with hyaline necrosis of the vessel walls, cellular infiltration, and some evidence of healing. By October 1941 his blood-pressure had risen to 180/110 and remained about this level throughout subsequent observation, while his urine still showed cells and casts as above, the sensory changes in the legs had disappeared, and the right knee-jerk had returned, but the erythrocyte sedimentation rate remained at 24 mm in one hour, and his white blood count was 8,000 per c mm, with a normal differential count. He finally took his discharge from hospital in November 1941, considerably improved, but still complaining of upper abdominal pain unchanged by diet and alkalis.

Although changes in the central nervous system are extremely rare, a painful peripheral neuritis, usually bilateral, and often asymmetrical, is a common finding, particularly in the lower limbs.

The general discomforts of a severe and continued toxic illness, with loss of weight, nausea and vomiting, malaise and joint pains, headache, pulmonary congestion with cough and dyspnoea, and a marked degree of cachexia and generalized muscle wasting are common, and in such cases death may close the picture without the development of more typical signs, the diagnosis being revealed only at autopsy. The patient most commonly dies in coma, which, though not infrequently uraemic, is more often apparently the end-result of a less specific chronic toxæmia. A stroke, or a gross haemorrhage elsewhere, is another frequent cause of death, while a secondary infection, usually a low-grade bronchopneumonia, is a common terminal finding.

It is questionable whether the attempt to systematize the disease into a small series of clinical types which has been made by von Schrotter (1899), Harbitz (1927), Hutinel, Coste, and Arnaudet (1930), and Lindberg (1931) is

O'Hare, 1939), and in addition to the specific changes of an acute arteritis and infarcts, glomerulonephritis has been recorded with increasing frequency since Brinkmann (1922) and Christeller (1926) added nephritis to Meyer's triad. Urinary changes are consequently frequent. Albuminuria is the commonest abnormality, being found in at least 64 per cent, while haematuria is somewhat less frequent. If the haematuria is due to glomerulonephritic changes, a few red cells may be constantly present, and accompanied by casts. More often slight haematuria is an occasional finding, related to successive renal infarcts.

Hypertension occurs in about 64 per cent of cases (Harris, Lynch, and O'Hare, 1939) and its frequent though not invariable relation to severe renal involvement suggests a possible origin in renal ischaemia. The raised blood-pressure reading is often of diagnostic importance and a diagnosis of polyarteritis should be considered in all cases of hypertension occurring acutely in children and in the earlier age periods. Particularly significant is the association of hypertension with continued pyrexia of unknown origin. Systolic figures above 200 mm of mercury are not infrequent, and we can confirm the accuracy of Bernstein's (1935) observation that the systolic pressure tends to oscillate widely between these high readings and figures in the upper zone of normality, and that a rapid rise to high readings is of bad prognostic significance and usually associated with severe renal involvement (Harris, Lynch, and O'Hare, 1939). Oedema is found in about half the recorded cases. It may be related to congestive cardiac failure which may be hypertensive, or may arise from failure of an ischaemic myocardium (Laubry, Soulié, and Lenègre, 1938). It may be renal, particularly in those cases with acute or subacute glomerulonephritic changes, or it may arise in association with the polymyositis which is found in over 50 per cent of cases (Boyd and Nussbaum, 1936) and is particularly common when the arteries of the limbs and the skeletal musculature are severely involved.

These are the commonest features of the disease—fever, leucocytosis, a raised erythrocyte sedimentation rate, albumin and blood in the urine, vascular hypertension, and oedema. The frequency with which the characteristic arterial changes are found in one or several of the abdominal viscera at autopsy (liver 66 per cent, alimentary tract 50 per cent, mesentery 41 per cent, pancreas 26 per cent (Gruber, 1926)) accounts for the common occurrence of abdominal pain. This is often violent, and maximal at the umbilicus or in the gall-bladder area. Spiegel (1936) gives generalized abdominal pain as the commonest mode of onset, and the association of such pain with anomalous features such as arthralgias, rheumatism, nephritis, hypertension, and heart failure should always suggest polyarteritis nodosa. Such abdominal pain may be a prolonged, severe and striking feature of the illness.

*Case 3 Severe and continued abdominal pain with melaena, fever, and polyneuritis*

A 35-year-old man was admitted to hospital in July 1941, complaining of upper abdominal pain, and pain down the back of the legs constantly present

for the previous four months. He had a past history of gonorrhoea at the age of 22 years and of the common illnesses of childhood. He was of good physique and had no abnormal physical signs in the heart or chest, and a normal blood-pressure. There was diffuse epigastric tenderness, several localized tender areas in both glutei medii and calves, and pain in the lumbar region and down the legs on straight leg raising. The right knee-jerk and both ankle-jerks were absent and there was bilateral patchy hypalgesia of stocking distribution. The plantar reflexes were flexor and the remainder of the central nervous system showed no abnormal findings. He had a haemoglobin of 80 per cent and a leucocytosis of 14,000 cells per c mm, predominantly polymorphonuclear cells, but with 5 per cent of eosinophil cells. His erythrocyte sedimentation rate was 50 mm in one hour, and his urine showed a trace of albumin, a few granular casts, and a moderate number of red blood cells and pus cells. All other investigations, including X-ray studies of the spine, barium meal and barium enema examinations, and examination of cerebrospinal fluid, were negative. He remained in hospital for six weeks, maintaining an irregular fever reaching a maximum of 100.5° F in the evenings, before he had a large melaena which reduced his haemoglobin to 53 per cent. After recovering from this a further barium meal was again normal, but in view of the combination of fever, polyneuritis and continuing abdominal pain, a muscle biopsy was performed on the right calf, and serial sections showed the typical changes of subacute polyarteritis nodosa with hyaline necrosis of the vessel walls, cellular infiltration, and some evidence of healing. By October 1941 his blood-pressure had risen to 180/110 and remained about this level throughout subsequent observation, while his urine still showed cells and casts as above, the sensory changes in the legs had disappeared, and the right knee-jerk had returned, but the erythrocyte sedimentation rate remained at 24 mm in one hour, and his white blood count was 8,000 per c mm, with a normal differential count. He finally took his discharge from hospital in November 1941, considerably improved, but still complaining of upper abdominal pain unchanged by diet and alkalis.

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The general discomforts of a severe and continued toxic illness, with loss of weight, nausea and vomiting, malaise and joint pains, headache, pulmonary congestion with cough and dyspnoea, and a marked degree of cachexia and generalized muscle wasting are common, and in such cases death may close the picture without the development of more typical signs, the diagnosis being revealed only at autopsy. The patient most commonly dies in coma, which, though not infrequently uraemic, is more often apparently the end-result of a less specific chronic toxæmia. A stroke, or a gross haemorrhage elsewhere, is another frequent cause of death, while a secondary infection, usually a low-grade bronchopneumonia, is a common terminal finding.

It is questionable whether the attempt to systematize the disease into a small series of clinical types which has been made by von Schrötter (1899), Harbitz (1927), Hutinel, Coste, and Arnaudet (1930), and Lindberg (1931) is

helpful, but it can be agreed that in many cases the general clinical picture is predominantly either that of

- (1) A non-specific subacute or chronic pyrexial wasting illness
- (2) An atypical abdominal illness of similar duration
- (3) A primary renal disease, or,
- (4) A combination of polyneuritic and polymyositic features

Often developments may occur during the course of the illness, the nature and distribution of which will indicate both the occurrence of a widespread pathological process and its primary site in the ramifications of the vascular tree. In view of the pathology of the disease the protean nature of such special manifestations may be anticipated, and it is likely that many remain to be described, but an analysis of those already on record, constantly bearing in mind their relation to the pathology of the disease as a whole, may help both to clarify our conception of the condition and to facilitate its recognition.

#### *The Cardiovascular System in Polyarteritis Nodosa*

The primary arterial changes are responsible for the development of subcutaneous nodules, which vary in size from a diameter of 4 to 12 mm., appear in crops, and may regress or persist for periods up to 18 months. They occasionally form discoloured phlebotenues, or ulcerate, and may appear on a base of extravasated subcutaneous blood. Pulsation of the nodules has been recorded a few times (Manges and Baehr, 1921, Matthes, 1928, Spiegel, 1936). Pathologically, aneurysm formation is not common, and in the absence of aneurysms close to the body surface subcutaneous nodules are very rare. Most commonly found along the course of temporal, brachial and intercostal arteries (Ophuls, 1923) they may occur at any site and have been found in the lips (Debré, Leroux, Lelong, and Gauthier-Villars, 1928) and tongue (Boyd and Nussbaum, 1936). Rupture of an aneurysm or a weakened arterial wall may result in haemorrhage from a variety of sites. Subcutaneous and intramuscular haematoma, retroperitoneal haematoma causing either an acute abdominal catastrophe or an intra-abdominal tumour, intraperitoneal, perirenal, pancreatic, cerebral, or subarachnoid bleeding, which may be acute, or possibly a slow leak producing a subacute meningitic picture, may all occur. Haemorrhage from a gastric artery may lead to haematemesis or melaena, and from an intestinal vessel to a dysenteric picture of bloody diarrhoea closely resembling ulcerative colitis. Similar processes may give rise to an acute haemorrhagic or chronic adhesive pleurisy or pericarditis, and haemopericardium from rupture of a coronary aneurysm may give rise to cardiac tamponade. In some cases focal signs are attributable to thrombosis in, rather than haemorrhage from, affected arteries, and the clinical picture of thrombosis of a cerebral artery or one of the main abdominal vessels (McCall and Pennock, 1944) may complicate the clinical picture. Following Meyer (1878) many authors have presumed that aneurysmal yielding of the vessel-wall is related to hypertension, but careful scrutiny of

recorded cases shows that the relation is not constant, aneurysm formation being recorded with normal blood-pressures, for example by Wordley (1923) and Vining (1938), while the majority even of hypertensive cases show neither subcutaneous nodules clinically nor aneurysmal formation pathologically. It seems that the formation of aneurysm is related rather to the failure of reparative processes to keep pace with destruction of the vessel-wall.

While it is clinically evident that some cases make a good recovery, Keegan (1925) and Jäger (1933) have described arteriosclerosis as a result of the healing of acute polyarteritis, and Jäger suggested that the condition may, in fact, be an important unrecognized cause of subsequent arterial degeneration. While there is evidence that this may be an occasional occurrence, in which residual renal damage may also play an important role, and while polyarteritis may be superadded to an existing arteriosclerosis, as in one of Middleton and McCarter's (1935) cases, or may itself produce the clinical picture of malignant hypertension, it is difficult to believe that the association suggested by Jäger is numerically important. Another occasional symptom referable directly to the vascular changes of polyarteritis is Raynaud's syndrome, with or without peripheral gangrene. Cases of this type have been reported by Frommel (1926), Cathala and Boegner (1928), Carr (1930), Bernstein (1935), and Cohen, Khine, and Young (1936). Pathologically, cardiac involvement is almost as common as renal involvement, coronary arteritis being found in 84 per cent of cases coming to autopsy (Harris, Lynch, and O'Hare, 1939). Nevertheless, except for tachycardia, which is frequently disproportionate to the degree of pyrexia, and terminal congestive failure in hypertensive cases, cardiac symptoms are not common.

*Case 4 A fatal case characterized by peripheral neuritis and congestive heart failure, leading to a diagnosis of beriberi*

A 41-year-old airman, en route for the Middle East in March 1943, was seized with cramping pains in both calves, of sudden onset, and accompanied by severe paraesthesia in the feet. He was admitted to hospital and returned to England in November of the same year with a diagnosis of infective polyneuritis. By this time he had begun to improve and to regain some of the considerable weight which he had lost. While on sick-leave, however, he developed oedema of the ankles and was admitted to hospital as a case of beriberi heart. Full investigation at this time revealed polyneuritis, cardiac enlargement, and a leucocytosis of 11,200 cells per c mm. On readmission to hospital in January 1944, he showed a scaly papular rash over the face, a muddy skin, tachycardia, general cardiac enlargement clinically and radiologically with thickened peripheral vessels, and a blood-pressure of 150/110. He had an improving severe peripheral neuritis with asymmetrical weakness, wasting, depression of deep reflexes, and hypalgesia and hypaesthesia limited to the distal parts of the lower extremities, which also showed pitting oedema and obliteration of the posterior tibial pulses. A chest X-ray showed marked congestive changes, and there was a mild anaemia of orthochromic type with 84 per cent of haemoglobin and 10,000 leucocytes per c mm, with a normal differential count. Erythrocyte sedimentation rate readings were

widely variable between nine and 45 mm in one hour (Westergren). Ophthalmoscopy revealed a gross arteriosclerotic retinitis with haemorrhages and exudate, but with no localized pathological changes in the arteries. The urine then and on several occasions throughout the illness was found to contain a small amount of albumin, a few red and white blood cells, and a few hyaline casts. At this stage the patient was seen by Sir Charles Symonds, who diagnosed peri-arteritis nodosa, on the strength of polyneuritis with hypertension and retinitis. The course of the illness was slowly downhill, with increasing congestive failure. The pulse-rate rose slowly from an average figure of 90 to 140, while oedema and dyspnoea increased, and early in February hepatic congestion and ascites were evident. Further cardiac enlargement occurred and on February 12 the blood-pressure was 165/130. From this time onwards, diuretics having failed, repeated abdominal paracenteses were performed. Early in May auricular fibrillation began, simultaneously rapid deterioration ensued, and the patient died on May 9 after several days of abdominal discomfort. Autopsy revealed generalized atherosclerosis of the usual type, cardiac hypertrophy, and the usual findings of congestive heart failure, with many old and recent infarcts in the lungs and kidneys. Microscopically there was a segmental necrotizing arteritis with cellular infiltration and many thromboses affecting the pulmonary, renal, and, to a less marked degree, the myocardial arterioles. The changes were characteristic of polyarteritis nodosa.

Lamb (1914) early drew attention to the frequency of silent coronary involvement, while the resultant ischaemic damage to the myocardium has been demonstrated by the occasional recording of electrocardiographic abnormalities (Åkesson, 1934, McCall and Pennock, 1944), and in particular by inversion or flattening of T1 and T2 (Master and Jaffe, 1933). A changing electrocardiographic picture has been suggested by Boyd and Nussbaum (1936) as an important point in the differential diagnosis of polyarteritis, and we have observed this phenomenon in one case with cardiac involvement, such a finding is rare in the diseases with which polyarteritis is usually confused. In view of the frequency of coronary involvement it is remarkable that anginal pain is not commoner. It has been recorded in a few cases, and on one occasion even in childhood (Nowak, 1933). There is suggestive evidence of a pathological relationship between the affection of the coronary vessels found in polyarteritis and the coronary arteritis described in acute rheumatism by Karsner and Bayless (1934).

As previously noted, a recent history of rheumatic infection is frequent, and, as well as Aschoff nodes, a rheumatic endocarditis and valvulitis may be found in association with the disease, as in cases recorded by Friedberg and Gross (1934), Spiegel (1936), and Grant (1939). The association of streptococcal infection both with rheumatism and with polyarteritis nodosa accounts for many of the cases of subacute bacterial endocarditis found in association with polyarteritis (Lamb, 1914, Siegmund, 1924, Mainzer and Joel, 1935), though the occurrence of gonococcal endocarditis (Helpern and Trubek, 1933) in one case shows again that the relation to streptococcal infection is not, as was at first believed, specific. A further cardiac finding to which attention has recently been drawn is an atypical verrucose endo-

carditis of Libman-Sacks type (Gross, 1932, Krahulik, Rosenthal, and Loughlin, 1935), while Banks (1941) and Krupp (1943) have adduced evidence of a common pathology in polyarteritis nodosa, the Libman-Sacks syndrome, disseminated lupus erythematosus (which is often associated with verrucose endocarditis and which had already been observed in polyarteritis by Cabot, 1938), and possibly also scleroderma and dermatomyositis. Microscopic examination of tissues in all these conditions shows an acute and subacute infiltrative arteritis, and these authors consider them all manifestations of a 'visceral angertis'. Again, the association of these conditions with preceding infection of varying types suggests that they may also partake of the nature of hypersensitive responses. Of the findings on blood examination, polymorphonuclear leucocytosis, anaemia, and occasional eosinophilia have already been mentioned. Purpura (Lamb, 1914, Bennett and Levine, 1929, Middleton and McCarter, 1935), both thrombocytopenic (Dunbar, 1936) and with normal platelet counts (Spiegel, 1936), has been described as an associated finding.

#### *Abdominal Symptoms    Surgical Aspects*

Microscopically, the intestinal wall is involved in at least half the cases and the frequency and importance of abdominal pain, a clinical feature in 57 per cent of case histories analysed by Harris, Lynch, and O'Hare (1939), has already been stressed, while the frequency of this symptom in polyarteritis has led to the suggestion by Spiegel (1936) that some cases of 'abdominal rheumatism' may be due to an analogous arterial change in acute rheumatism. The pain in polyarteritis nodosa, discussed at some length by Roux (1939), is often diffuse or umbilical and may arise from vascular changes both in the wall of the alimentary tract and in the mesentery. The association of such symptoms with marked emaciation may lead to an erroneous diagnosis of carcinoma of the stomach, as in one of our own cases, where signs of subacute intestinal obstruction subsequently ensued (Miller and Nelson, 1945). Pathologically the submucous and muscular coats are first involved, but later erosion or chronic ulceration of the overlying mucosal surface, secondary to ischaemic changes, may lead to the finding of occult blood in the stools and even to bloody diarrhoea, or to gangrene of the bowel wall (Lorenz, 1891, Versé, 1907, Harbitz, 1927, Spiegel, 1936). Lelong, Rachet, Foulon, and Lelong (1938), Mondor, Dueroquet, and Olivier (1939), and Felsen (1941) have described sigmoidoscopic findings in patients with polyarteritis nodosa. These consist of horizontal, parallel, linear streaking with localized vascular dilatations probably due to a thrombosing vasculitis and described by one author as 'tapioca-like'.

Erosions or ulcers in stomach- or bowel-wall may perforate (Versé, 1907, Krahulik, Rosenthal, and Loughlin, 1935, Spiegel, 1936, Miller and Nelson, 1945), causing fatal peritonitis or a subdiaphragmatic abscess (Spiegel, 1936). In other cases peritonitis of a more chronic type may occur as part of a



polyserositic picture Abdominal pain in polyarteritis nodosa may, however, be localized to regions characteristic of inflammatory conditions in particular viscera, and such pain may be due either to actual involvement of a hollow viscus by arteritis, or to simulation of a similar clinical picture by a localized retroperitoneal haematoma Of Spiegel's (1936) 17 cases, abdominal pain led to laparotomy before diagnosis in six, appendicitis being diagnosed and appendicectomy being performed in four Similar cases with a clinical picture of acute or subacute appendicitis have been described by Benedict (1907), Lamb (1914), Plaut (1931), Friedberg and Gross (1934), and Druss and Maybaum (1934), in Plaut's case such a finding was associated with polyarteritis also in the uterine adnexa In several of these cases and also in one case of vasectomy (Gagstatter, 1934), microscopic examination of tissue removed at operation led to an ante-mortem diagnosis Baló and Nachtnebel (1929) reported a case with a clinical picture of appendicitis due to a localized retroperitoneal haematoma

Microscopic examination of a gall-bladder removed after symptoms of acute cholecystitis (Klotz, 1917, Grüber, 1926, Singer, 1927, Middleton and McCarter, 1935, Spalding, 1940, Naegeli, 1940) may also lead to a correct diagnosis Grüber suggested that involvement of vessels in the wall of the gall-bladder may lead to biliary stasis and secondary infection, and massive haemorrhage into the gall-bladder has been recorded as a sequel Symptoms arising from the liver itself are less common, and although it is pathologically involved in about two-thirds of cases, icterus is much less frequent, and was noted by Harris, Lynch, and O'Hare (1939) in only 12 per cent Pass (1935) stated that polyarteritis nodosa is the commonest cause of hepatic infarction, while subcapsular haemorrhages may cause hepatic pain and may rupture into the peritoneal cavity (Klotz, 1917, Grant, 1939).

Pathologically, pancreatic involvement is frequent, and haemorrhages, necroses, infarcts, diffuse fibrosis, or involvement by retroperitoneal haematoma may be found (Klotz, 1917, Singer, 1927, and Spiegel, 1936) The clinical picture varies in acuteness from one of vague upper abdominal discomfort to that of catastrophic haemorrhagic pancreatitis, while Middleton and McCarter (1935) have described a case with a subacute course and an abnormal sugar tolerance curve

Splenic involvement is less common, occurring in less than a third of cases examined *post mortem*, while although infarction and perisplenitis may occur, splenic pain is uncommon and splenomegaly distinctly rare

Renal involvement is not invariable, and even in fully developed and hypertensive cases the urine may be repeatedly normal, a negative finding which has several times in our own experience led to failure to reach a correct diagnosis Nevertheless, the best pathological studies show that the kidneys are involved in at least 70 per cent of cases, with infarcts in 55 per cent and glomerulonephritis in at least a third (Gruber, 1926) The urinary findings reflecting these changes have already been discussed Krupp (1943)

pointed out that in visceral angertis, in which category, as already noted, he included polyarteritis nodosa, disseminated lupus erythematosus, and the Libman-Sacks syndrome, a study of the urinary sediment shows a unique microscopic picture in that red blood cells, red cell casts, fatty casts, and 'broad' casts are all found together, a combination not usually seen at any stage in the development of the more usual cases of glomerulonephritis. In addition to these urinary findings, anuria has been recorded (Rolnick and Davidsohn, 1942), and in one case was due to cortical necrosis of the kidney (Wordley, 1923). The multiple renal infarcts so often seen have a pathological importance as well as clinical significance as the cause of recurrent microscopic haematuria. Several pathological papers point out that the gross finding of such infarcts at autopsy in cases without bacterial endocarditis is extremely uncommon, and that it should always give rise to a strong suspicion of polyarteritis nodosa.

Somewhat less frequent in polyarteritis nodosa is the clinical picture of a surgical kidney condition. Haematuria may be profuse and unilateral, simulating growth (Powell and Pritchard, 1932), renal colic may occur (Gray, 1932, Hauser, 1934) or symptoms may imitate a vesical growth (Kimmelsiel, 1927), while a combination of general signs of sepsis and local renal symptoms may point to a carbuncle of the kidney (Keegan, 1925, Gray, 1932). In one of our own cases a renal neoplasm was closely simulated by a large retroperitoneal haematoma.

*Case 5 Polyarteritis nodosa simulating a renal tumour, diagnosis revealed by nephrectomy*

A 32-year-old airman, with no significant past or family history began to complain of stiffness and pain in the legs and calves in August 1945. Ten days previously he had had an injection of anti-tetanus and anti-typhoid vaccines, his fifth in three years, which was unaccompanied by immediate toxic reaction. Notes on admission to hospital describe a sick man with severe pain and marked tenderness in both calves, and little to show on examination other than a high erythrocyte sedimentation rate (82 mm in one hour). There was no response to salicylates. The erythrocyte sedimentation rate remained high, and five days later he developed a moderately severe generalized urticaria followed by the gradual onset of nausea, vomiting, hiccough, and diffuse abdominal pain. The pain became so severe that a surgeon considered the possibilities of acute pancreatitis or mesenteric thrombosis. The patient showed high pyrexia (101° F) and a leucocytosis of 18,600 cells per c mm, polymorphonuclear cells predominating, and occasional pus cells and casts in the urine. He remained critically ill for 10 days, but there were no clear indications for laparotomy and he slowly recovered, simultaneously developing a mild symmetrical polyneuritis affecting the lower limbs. The erythrocyte sedimentation rate and leucocytes remained high, and despite general improvement there were periodic recurrences of abdominal pain and vomiting. Radiological studies and blood chemistry remained normal, but for the first time an appreciable number of red and white blood cells and granular casts began to appear in the urine, while the haemoglobin showed a gradual fall from 85 to 55 per cent the white count remaining between 6,000 and 10,000 per c mm. On November 3, 1945, he

showed eosinophilia in one count (7 per cent of 9,800 white blood cells per c mm), otherwise his differential count was normal. His polyneuritic signs showed rapid improvement, but about this time he began to complain of increasing pain in the left flank and lower left chest. The possibility of a renal tumour was considered and this was supported when a barium enema showed forward displacement of the descending colon by a posteriorly placed tumour, an intravenous pyclogram showed enlargement of the left kidney with a large calyceal pelvic filling defect, and finally palpation revealed a tumour deeply situated in the left flank. On January 16, 1946, operation (nephrectomy) revealed a kidney disorganized by a large retroperitoneal haematoma extending downwards towards the pelvis and with many adhesions. The pathological report on the kidney specimen described a subacute infiltrative arteritis showing healing and fibrosis, with superadded mild glomerulonephritic changes. A similar appearance was shown by muscle biopsy, where hyaline changes and endarteritis were also evident. His condition then rapidly improved. The haemoglobin, which fell for some time as low as 40 per cent, responded to iron administration, and rose to 82 per cent. The blood-pressure remained high (180/110 to 160/110), the urine contained red and white cells and granular casts, and at the time of writing there was still moderate nitrogen retention with a blood-urea averaging 60 mg. per 100 c c. The only symptoms remaining were moderate postural oedema and breathlessness. Despite the histological evidence of healing in this case, the prognosis was considered poor in view of the involvement of his remaining kidney.

Surgical aspects in general have been reviewed by Mondor, Ducroquet, and Olivier (1939), Spalding (1940), and Allen (1940). The first-named authors, in addition to dealing with the commoner abdominal symptomatology, described and illustrated the treatment of deformities resulting from peripheral gangrene in polyarteritis. Diagnosis before microscopic examination of tissues removed, as in Manges and Bachr's (1921) case, where the surgeon (Buerger) recognized the condition from the gross appearance of mesenteric arteries, is exceptional. The usual story is that of a subacute abdominal condition not quite typical of inflammatory involvement of any particular viscus, leading to removal of an organ, usually with recognition of the condition after microscopic examination, or that the condition is recognized because of the patient's failure to improve after operation, and the subsequent development of symptoms farther afield. Retrospective scrutiny of these surgical cases reveals frequent clues to correct diagnosis in the presence of preceding or coincidental symptoms impossible of reference to a localized abdominal condition, for example, peripheral neuritis, sore throat, arthralgias, fugitive erythema and urticaria, and asthma, the significance of which was not realized at the time. These cases illustrate the importance of two points in the recognition of polyarteritis. First, the original erroneous diagnosis made in cases subsequently proved to be polyarteritis nodosa is frequently that of an atypical form of some other commoner condition, such a diagnosis often fails to carry conviction even in the mind of the clinician concerned, who feels instinctively that there is something wrong with it. Secondly, the difficulty of attributing the clinician's scattered findings to a single patho-

logical process may lead to multiple diagnoses, and it is only when the multiplicity of the pathological conditions postulated becomes unreasonable that polyarteritis is thought of. One of our own cases illustrates both these difficulties well.

*Case 6 A fatal case simulating abdominal malignant disease, and with hypertensive fits, polyneuritis, and a diagnosis revealed by retinal changes*

A 34-year-old airman, with a past history of eczema and urticaria and under treatment for syphilis, in May 1945 developed generalized joint pains unresponsive to salicylates, but clearing after cessation of arsenical medication. In August, 24 hours after further trial doses of neoarsphenamine, he developed constant, severe, central epigastric pain accompanied by marked anorexia and vomiting. Retrospective inquiries showed that the onset of this was associated with flitting arthralgias and aching pain down both legs. His pain was severe, loss of weight was rapid, and anorexia absolute, and when he was admitted to hospital two weeks later he was suspected of having either a penetrating peptic ulcer or a carcinoma of the stomach, an error also made in the case of Cameron and Laidlaw (1918). Full examination revealed only marked loss of weight and generalized epigastric tenderness. Barium meal examination, gastric analysis, and occult blood tests proved negative, and his pain became more severe despite treatment. In view of the negative investigations for gastro-intestinal disease the suspicion of pancreatic carcinoma was raised. Tests for pancreatic function, however, proved negative. The cerebrospinal fluid remained normal and the erythrocyte sedimentation rate was eight mm in one hour. There was occasional evening pyrexia of 99°F. On September 14, 1945, he had a generalized epileptic fit followed by severe headache and vomiting. At first intracranial metastases from a cryptogenic carcinoma were suspected, but his blood-pressure was found to be 210/120, while the cerebrospinal fluid remained normal in composition, though with a raised pressure. Radiological examinations of skull, chest, and abdomen, and blood chemistry gave no clue to the essential nature of the disease, but his white blood cells rose to 10,000 per c mm, and there were occasional red cells and pus cells in the urine. Within a few days the margins of the left optic disk became blurred and a slit haemorrhage appeared in the retina. Despite supportive treatment the patient went rapidly downhill. On September 26, 1945, he had repeated epileptic fits followed by coma which lasted for more than 24 hours, and on recovery the knee- and ankle-jerks were found to have disappeared, without marked sensory loss or diminution of motor power. The erythrocyte sedimentation rate was 45 mm in one hour, white blood cells 32,000 per c mm, and differential count normal. The hypertension and albuminuria persisted. These findings strongly suggested a diagnosis of polyarteritis nodosa. This was confirmed by the gradual development of characteristic ocular findings, pale perivascular hillocks of choroidal exudate, retinal detachments, irregularity in the calibre of retinal vessels, the whole picture variable and shading off into a characteristic albuminuric retinitis. The diagnosis was confirmed by serial sections of a biopsy specimen of calf muscle. Marked cachexia and weakness without anaemia ensued. There was no pyrexia at any time except for two days after the fits of September 29, 1945, and death followed on October 30, 1945. Autopsy revealed acute and subacute polyarteritis nodosa involving kidneys, mesentery, peripheral nerves, and skeletal musculature, but sparing the central nervous system.

*Neurological Features and Ocular Findings*

The occurrence of spontaneous subarachnoid or cerebral haemorrhage from ruptured aneurysms has already been mentioned. Involvement of the intimate vasculature of the central nervous system is relatively uncommon, the figures for this varying from 8 per cent (Gruber, 1926) to 20 per cent (Foster and Malamud, 1941). In view of the relative infrequency of careful histological examination of brain tissues in these cases, most of the figures quoted are probably too low. Such cases have been described in detail by Runge and Melzer (1930), whose patient showed bulbar symptoms, dysarthria, cerebellar ataxia, bilateral pyramidal lesions, and mental changes, and by Foster and Malamud (1941), whose cases presented meningeal irritation, diplopia, hemiparesis, and dementia. Pathologically, the arterial involvement is usually maximal in the meninges and the marginal zone, and it may be localized to certain areas of the cerebral vascular field or spinal cord. Somewhat similar cases of meningeal and cortical involvement are reported by Baló (1926), Baló and Nachtnebel (1929), Erlandsson (1931), Krahulik, Rosenthal, and Loughlin (1935), Urechia (1941), and Maxwell and Maxson (1941). A meningitic picture without histological findings is recorded by Bennett and Levine (1929), and meningism is a frequent feature in childhood cases. Kourilsky, Gracin, Bertrand, and Hinglais (1938) recorded a remarkably subacute course with remitting paraplegia and quadriplegia in a case characterized also by a skin eruption. Urechia and Elekes (1934) refer to other cases showing paraplegia, in some instances associated with bulbar palsies and cranial nerve lesions. Focal nervous signs are very variable, and the following table, adapted from Foster and Malamud (1941), demonstrates the more important signs found in 65 cases of polyarteritis with central nervous system involvement.

*Neurological Signs in 65 Cases of Polyarteritis with Involvement of the Central Nervous System*

(From a review of 300 cases by Foster and Malamud, 1941)

Generalized convulsions	24	Increased C S F pressure	8
Meningeal irritation	14	Increased C S F. protein	6
Organic brain syndrome	14	Subarachnoid bleeding	7
Hemiplegia	11	Extra-ocular muscle palsies	5
Sluggish pupillary light reaction	11	Extrapyramidal signs	5
Amisocoria	10	Papilloedema	4
Cerebellar signs	9	Optic atrophy	4
Jacksonian fits	8	Nystagmus	4

The probable occurrence of cerebral changes in less fully investigated cases is suggested both by the occasional finding of changes in the cerebral arteries in cases without relevant symptomatology, and by the incidence of fits, which occur in no less than 15 per cent of cases (Harris, Lynch, and O'Hare, 1939). These are usually generalized epileptic attacks, and in one of our own cases approximated to status epilepticus, followed by coma lasting for 48 hours.

While in some cases the fits may be considered hypertensive, the occurrence of cases with a local onset or a Jacksonian syndrome (Krahulik, Rosenthal, and Loughlin, 1935, Bennett and Levine, 1929), suggests a local pathology involving cortical vessels. Delirium or coma are common and are not limited to cases showing uraemia, while confusional and dementing features have been several times recorded.

Pupillary changes, chiefly inequality with normally retained reactions, are described by Spiegel (1936), Maxwell and Maxson (1941), and Miller and Nelson (1945), and involvement of the third, seventh, and eighth cranial nerves is several times on record. Foster and Malamud (1941) report diplopia, while Böck (1929) records clinical evidence for, and Tertsch (1935) pathological proof of, involvement of the vessels of the extrinsic ocular muscles. Neale and Whitfield's (1934) case showed conjugate deviation of the eyes, in addition to choreiform movements.

*Case 7. A girl of 16 years with subcutaneous nodules, peripheral gangrene, cranial nerve lesions, and involvement of the central nervous system evident in spastic quadriplegia, nystagmus, and organic mental changes*

A 16-year-old girl was admitted to hospital on January 26, 1942, with a past history of swelling of the right knee recurring for three years from the age of 11 years, and of repeated attacks of conjunctivitis unrelieved by tonsillectomy in 1940. Two years before admission she had had a moderately severe febrile asymmetrical polyneuritis, of gradual onset, affecting all four limbs, and associated with fugitive erythemata. Signs of this neuritis were still present in December 1940, when she developed a sudden complete spastic paraplegia with retention of urine and loss of phonation. After some weeks, voluntary power gradually returned, her voice became stronger, and she began to regain control of her bladder, but in March 1941 fever, dizziness, and bilateral visual impairment ensued. In April she had a severe attack of headache, vomiting, and visual failure, with which was associated nystagmus in all directions. This slowly subsided, but marked dysphagia, diplopia due to a right abducens paralysis, and left facial weakness followed, while in August she developed retention of urine and gangrene of the second toe of the left foot. From this time until admission to hospital six months later, she was febrile and had a rapid pulse, while her neurological symptoms fluctuated. Sphincter control improved, but she was inattentive, apathetic, and often incontinent. On admission she was lethargic and showed a spastic quadriplegia, coarse nystagmus with a rotary component on upward and lateral gaze, paresis of the right temporal muscle, bilateral palatal weakness, gangrene of the second left toe, and a few small subcutaneous nodules in each popliteal space. There were no abnormal signs in the other systems. During the next four months in hospital she remained pyrexial, with a rapid pulse and recurrent microscopic haematuria. The spleen became palpable, and the erythrocyte sedimentation rate remained about 100 mm in one hour, while a moderate microcytic anaemia developed and the gangrenous toe began to separate. The white blood cells and the cerebrospinal fluid were normal. At this stage a diagnosis of polyarteritis nodosa was considered. A specimen of quadriceps muscle contained no vessels adequate for examination, but sections of the amputated gangrenous toe revealed changes indicating healing polyarteritis nodosa in the arterioles, and secondary degeneration and fibrosis of nerve-bundles. Incidentally, this amputation was remarkable for the

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Jacksonian fits	8	Nystagmus	4

The probable occurrence of cerebral changes in less fully investigated cases is suggested both by the occasional finding of changes in the cerebral arteries in cases without relevant symptomatology, and by the incidence of fits, which occur in no less than 15 per cent of cases (Harris, Lynch, and O'Hare, 1939). These are usually generalized epileptic attacks, and in one of our own cases approximated to status epilepticus, followed by coma lasting for 48 hours.

and the findings are usually remittent and often asymmetrical Wohlwill (1923) was the first to demonstrate that these changes may depend on nerve ischaemia following an obliterative arteritis of the vasa nervorum, and in these cases, probably the majority, the picture of successive involvement of peripheral nerve trunks is that of a mononeuritis multiplex (Kernohan and Woltman, 1938) Naegeli (1940) reported polyarteritis nodosa as a cause of bilateral 'sciatica', and in one of our own cases (Miller and Nelson, 1945) the combination of sacral root signs with a positive Wassermann reaction lead to a diagnosis of gumma of the cauda equina Marinesco and Draganesco (1927) also described a case with root signs Most cases of peripheral neuritis in polyarteritis nodosa are probably of this type, and the frequency with which changes have been found in the vasa nervorum appears proportional to the thoroughness with which the peripheral nerves have been pathologically investigated The undoubted dependence of these cases of peripheral neuritis on peripheral vascular occlusion gives grounds for interesting speculation as to the possible role of vascular factors in the genesis of other cases of 'infective' polyneuritis, while one case in which polyarteritis nodosa involving the central nervous system was accompanied by widespread demyelination (Baló, 1926) raises the same problem in relation to the central nervous system There is some evidence that a toxic polyneuritis can occur in polyarteritis nodosa (Baló, 1926, Kimmelstiel, 1927, Kulkow, 1941), and the first of these authors postulated a relationship between pancreatic and polyneuritic involvement In one of our own patients (Case 6) we have observed the simultaneous disappearance of knee and ankle jerks, with rapid wasting, symmetrical motor weakness, and a complete absence of sensory loss Clinically we would have considered that such a case fell into the class described by these authors Nevertheless, microscopic examination of peripheral nerves showed an early stage of characteristic involvement of vasa nervorum

#### *The Respiratory System and Radiological Aspects*

In contrast with the abdominal findings, chest pain is a rarity in polyarteritis, and when it does occur is usually the result of pleurisy related to pulmonary infarctions, pericarditis, or an intercostal neuritis Earlier observers considered changes in the pulmonary parenchyma rare, and most of the relevant literature dates from the last decade Arkin (1930), though listing transient pneumonic infiltrations, haemorrhagic infarcts, and atelectasis as occasional findings, omitted reference to the frequency of pulmonary involvement in his numerical analysis of organ pathology Ophuls (1923) and Monckeberg (1931) drew attention, however, to the occurrence of specific arterial changes in the lungs Herrman (1933) described radiological findings of a diffuse perivascular infiltration spreading out from the hila, with confluent opacities of moderate density, and changes characteristically variable in intensity, terminating in infarcts and bilateral effusion He demonstrated the relation of these findings to the characteristic changes in bronchial and



complete absence of bleeding, and healing was normal. The further progress of the case is known only in outline. After a period of considerable improvement, the patient left hospital in May 1942, but died in September of the same year. Autopsy findings are not available.

Considerable literature has grown round the ophthalmological aspects of polyarteritis nodosa. Muller (1899) first described the microscopic appearance of polyarteritis nodosa of the retinal arteries. Since this time Friedenwald and Roncs (1931) alone have noted pathological retinal artery involvement, and in their case it was minimal, but many others have described such changes in the choroidal vessels at autopsy (Goldstein and Wexler, 1937, Böck, 1929, Helpern and Trubek, 1933, Gjertz, Nordlöw, and Svenmar, 1939). Clinically, many authors have described the gradual development of arteriosclerotic retinitis during the course of polyarteritis nodosa, but the occasional asymmetry of ocular findings, extending even to unilateral papilloedema and optic atrophy (King, 1935) has suggested a possible relation of the ocular appearances to local pathological factors. Bock (1932) described massive retinal detachment, which alone is sufficient to implicate factors other than hypertension, and Goldstein and Wexler (1937) described characteristic arteritis of the vessels of the optic nerves.

Sampson (1945) achieved an interesting synthesis of the pathological and clinical observations previously made, describing a picture which he considered characteristic of polyarteritis nodosa, showing multiple and variable exudative retinal detachment, perivascular hillocks of pale choroidal exudate resembling miliary tubercles, and unevenness in the calibre of retinal vessels, the whole shading off into a picture of gross arteriosclerotic retinitis. This picture closely follows the appearance forecast by Goldstein and Wexler (1937) on the basis of their microscopic studies. It will be seen that these findings share with those in other systems in this disease the usual characteristics of variability and remission. In a second case seen by us in this hospital, Sampson was able to make a correct ante-mortem diagnosis by the observation of similar ophthalmoscopic appearances to those described above. Other, and rarer, ocular findings include occlusion of the central artery of the retina (Helpern and Trubek, 1933, Bernstein, 1935), proptosis, iridocyclitis, episcleritis, and chemosis of the conjunctiva, conjunctivitis is a common occurrence during the course of the disease.

Peripheral neuritis, reviewed by Kernohan and Woltman (1938), is one of the commonest features of the condition, being noted in at least 20 per cent of recorded cases, and it was recently described by Jones (1940) in nine of 14 personal cases. With the polymyositis which often accompanies it, polyneuritis is responsible for the fact, so often stressed, particularly by French authors, that polyarteritis is a very painful disease. The neuritic and myositic pains and paraesthesia are most frequent and severe in the limbs, but they may occur anywhere in the trunk and they may have a root distribution. Although brachial neuritis and bilateral wrist drop with muscular wasting and fibrillation have been reported, the lower limbs are most often involved,

lymphnodes in the cervical, epitrochlear, and inguinal regions. There was a gross symmetrical polyneuritis with nystagmus and slight bilateral ptosis. The upper extremities showed loss of power and diminution of deep reflexes, bilateral wrist drop, and striking impairment of proprioceptive sensibility leading to marked ataxia. Superficial sensation was little affected. The legs were similarly although less severely affected, the knee-jerks were absent and the ankle-jerks depressed, abdominal reflexes absent, and plantar responses flexor. Ancillary investigations revealed a mild orthochromic anaemia with 85 per cent of haemoglobin and 35,000 leucocytes per c mm, of which 73 per cent were eosinophil polymorphonuclear cells. This eosinophilia was reflected in the sternal marrow, which yielded—

Myeloblasts	1 per cent
Neutrophil myelocytes	17 " "
Neutrophil polymorphonuclears	7 " "
Eosinophil myelocytes	40 " "
Eosinophil polymorphonuclears	15 " "
Basophil myelocytes	5 " "
Lymphocytes	1 " "
Erythroblasts	5 " "
Normoblasts	8 " "
Megaloblasts	1 " "

The urine, faeces, and cerebrospinal fluid were normal, but a chest X-ray showed moderate diffuse pulmonary fibrosis and emphysema. During the first weeks of August the polyneuritis and mental condition began to show some improvement, but he remained ill and toxic and began to run an irregular temperature up to 100.4° F. A leucocytosis of 23,000 per c mm was the lowest figure recorded, and over 66 per cent of eosinophil cells were constantly present. An X-ray of muscles showed no evidence of cysticercosis. From 8.8.45 to 23.8.45, when he died, he went slowly downhill with epistaxis, generalized purpuric rashes (platelets 150,000 per c mm on 13.8.45), albuminuria, and later slight haematuria, continued fever, and delirium. Autopsy revealed the diagnosis. Grossly there were many haemorrhagic subpericardial nodules, multiple infarcts of the spleen and kidneys, bronchitis, hilar fibrosis, and patchy bronchopneumonia. Microscopically, typical lesions of polyarteritis nodosa were found in the heart, kidneys, skeletal muscles, sciatic nerve, and pulmonary vessels. The lung sections also showed chronic bronchitic changes and marked eosinophilic infiltration in the bronchopneumonic areas.

#### *Skin Manifestations*

The subcutaneous nodules which represent the primary arterial lesion have already been discussed. Other skin manifestations are frequent and remarkably polymorphic in character. Reviews of the condition from this aspect have been published by Alkiewicz (1933), Crosti (1935), Goldschlag and von Chwalibogowsky (1935), Matras (1938), and Ketron and Bernstein (1939). Fugitive erythemata, including scarlatiniform eruptions, urticaria, and purpura, are the most commonly encountered lesions, but macular and papular rashes are not infrequent, while angioneurotic oedema, vesiculation, and bullous eruptions have been recorded. These last two may become necrotic and ulcerate, involving large areas of skin, and being one cause of the peripheral gangrene frequently noted. They may leave serious deformities from

pulmonary vessels demonstrated at autopsy Wiener (1933) and Weir (1939) have recorded identical radiological pictures, and the last author described miliary foci of organizing pneumonia with cellular infiltration and a local eosinophilia, a pathological finding previously noted by other authors including Curtis and Coffey (1934) In Sandler's (1938) report terminal miliary abscesses were superimposed in a fatal case Elkeles and Glynn (1944) reviewed the literature of pulmonary involvement in polyarteritis nodosa, and reported two further cases somewhat similar to those previously described, showing increased vascular markings particularly at the hila, and, in the lower lobes, transitory infiltrations regressing without residual abnormality The changes spared the periphery of the lungs and were probably due to a combination of perivascular infiltration, oedema, and haemorrhage Such transitory pulmonary infiltrations, occurring in the absence of cardiac failure as a possible cause, and associated with eosinophilia, are strikingly similar to the findings of Löffler's syndrome (Löffler, 1936), which may be associated not only with evidence of local and general hypersensitive reactions to preceding infections or infestations, but also with focal eosinophilic infiltrations elsewhere in the body Harkavy (1941) reported similar pulmonary findings in a series of asthmatic patients, in one case progressing to a fully developed picture of polyarteritis nodosa He demonstrated that the pulmonary changes probably arise on the basis of local vascular damage of allergic origin, and drew attention to a possible association of polyarteritis with the syndrome resembling thrombo-angitis produced in the limb vasculature by experimental sensitization to tobacco proteins Attention was drawn to the pathological similarity of thrombo-angitis and polyarteritis by Bruetsch (1942) and others, and despite the histological objections put forward by Scheinker (1945), the similarities appear more striking than the differences Elkeles and Glynn (1944) pointed to the involvement of pulmonary vasculature in Rich's (1942) experimental rabbits, suggesting that the vascular nature of the lung fields render them an important part of the anaphylactic 'shock organ' in polyarteritis and other hypersensitive states

*Case 8 A patient with asthmatic attacks as an early symptom and with polyneuritis, marked eosinophilia, purpura, and terminal eosinophilic bronchopneumonia*

A 56-year-old man had five weeks of nasal catarrh and bronchitis in February 1945 This was followed by the onset of progressive exertional dyspnoea, and later by attacks of paroxysmal nocturnal dyspnoea, diagnosed in June as bronchial asthma From this time he complained of increasing abdominal and chest pains, severe enough to make him take to his bed, and of muscular pains and paraesthesia in the extremities The pains led to sleeplessness and loss of weight He was admitted to hospital on July 30 He was ill, apathetic, and apyrexial, with a pulse-rate of 100 and a normal cardiovascular system Examination of the chest showed prolonged expiration and scattered rhonchi There was no tumour, tenderness, or rigidity on abdominal palpation, but there was moderate non-tender enlargement of

appetite returned, and he began to put on weight. His skin eruptions healed and joint pains and swelling disappeared, while the white blood-count fell to normal. He was discharged from hospital, well, on December 3, 1943.

### *Polyarteritis in Childhood*

Paediatric aspects of polyarteritis nodosa have been dealt with by Rothstein and Welt (1933), Vining (1938), Keith and Baggenstoss (1941), and Coe, Reisman, and De Hoff (1941). Although the condition is found at all ages it is less frequent in childhood than in adult life. Thus, until 1933 only 23 cases had been recorded in children up to the age of 15 years, as compared with 195 adult cases, an incidence of 11.8 per cent (Rothstein and Welt, 1933), and 17 of these cases occurred between the ages of 10 and 15 years. The pathological processes being similar at all ages, the clinical manifestations show a corresponding similarity, but as in many other childhood diseases the clinical picture appears more often to declare itself frankly, to show a more acute course and greater constitutional reaction, and to be less often complicated by degenerative diseases. While subacute and chronic cases, particularly in association with rheumatic infection, are frequent, some cases are very acute and one indeed has been recorded with death within four hours of the onset (Thinnes, 1924). A study of the childhood cases reveals a higher incidence of convulsions (in 50 per cent of Rothstein and Welt's cases, as opposed to 15 per cent of the cases at all ages analysed by Harris, Lynch, and O'Hare (1939)), and a greater prominence of lymphadenopathy, purpura and skin eruptions in general, peripheral gangrene, and arthralgias. Otherwise the clinical course and the prognosis are not in any way dissimilar from those found in adult life.

### *Summary*

The clinical manifestations of polyarteritis nodosa as recorded in the more important world literature are detailed. The pathology of the condition is briefly presented, and recent work on aetiology reviewed. Many clinical features lend support to the experimental view that the condition represents a non-specific hypersensitive reaction of anaphylactic type to a variety of antigens. There is suggestive evidence on clinical and pathological grounds that a number of ill-understood conditions, of which lupus erythematosus, Löffler's syndrome, and Libman-Sacks disease are the most important, may represent a localized form of acute arteritis, analogous in nature and aetiology to polyarteritis nodosa. The commoner clinical manifestations in the various systems are discussed, and nine cases briefly described. The infrequency of signs often considered typical, the nature and behaviour of vascular hypertension, the simulation of surgical conditions in the abdomen, urinary findings, ophthalmoscopic appearances, the pathogenesis of polyneuritis, radiological findings, and the behaviour of the disease in children are discussed.

tissue destruction and contracture. In addition to peripheral gangrene, decalcification in the bony skeleton of the hands and feet may be similarly related to a gradual reduction of peripheral blood supply, and has been discussed by Kourilsky, Gracín, Bertrand, and Hinglais (1938) and Mondor, Dueroquet, and Olivier (1939). More specific types of skin eruptions have been occasionally recorded, and in this connexion a relationship to erythema nodosum (Klotz, 1917, Ophüls, 1923, Spiegel, 1936) and lupus erythematosus (Cabot, 1938, Krupp, 1943) seems to be well substantiated. The majority of skin manifestations found in polyarteritis nodosa are of hypersensitive type, and lend further weight to the allergic hypothesis of aetiology.

Case 9 *A recovered case with skin necrosis and oedema, simulating pyaemia*

A 23-year-old Air Gunner was taken acutely ill in May 1943, with pain and swelling in the left elbow and other joints, and chest pain. He had a temperature of 102° F. and a pulse-rate varying between 100 and 124. Multiple, raised, erythematous patches appeared on the legs, arms, and abdomen, and in the course of a few days many of these became grey and necrotic at the centre. He failed to respond to a course of sulphathiazole and became critically ill, with moderate splenic enlargement the only other abnormal finding. On the strength of an isolated positive blood-culture a tentative diagnosis of *Staphylococcus aureus* pyaemia was made, though no initial focus could be found on careful search. He showed a white blood count of 49,600 cells per c mm with polymorphonuclear cells predominating, and this blood-picture was maintained throughout the illness without eosinophilia being found at any time. He was then given a course of penicillin, receiving approximately 1,000,000 units during the fourth week in June, but this appeared to have no effect on the course of the illness. He remained pyrexial, developed a remittent parotitis and cellulitis of the neck, and a marked degree of profuse postural oedema, though his skin eruptions decreased in number and severity. His oedema was at first considered largely inflammatory in origin, but he showed a striking fall in serum-protein, and a reversal of the albumin-globulin ratio (serum-albumin 2.07 gm per 100 c c, serum-globulin 3.59 gm per 100 c c), and his oedema was much improved by concentrated plasma transfusions. His urine showed only occasional pus cells, while his heart and electrocardiogram, X-rays of chest and bones, blood-urea, and other ancillary tests remained normal, and there was no vascular hypertension. Repeated blood-cultures were negative, and as the originally isolated staphylococcus proved coagulase-negative the diagnosis of staphylococcal pyaemia could not be sustained. A second course of sulphathiazole was given, without effect. Early in August a new crop of skin eruptions occurred and muscle biopsy was performed. Histologically this showed an acute and subacute arteritis and peri-arteritis with necrosis of vessel wall and infiltration with polymorphs, eosinophils, and leucocytes, diagnosed as polyarteritis nodosa by several pathologists. Early in September his condition became worse. He was losing weight and had anorexia, with a high swinging temperature and repeated crops of tender, erythematous, raised patches over the trunk and limbs, joint pains, accompanied by peri-articular swelling and limitation of movement, and transient pericardial friction. He continued thus throughout September and most of October. Towards the end of the latter month he showed a sudden and remarkable improvement, and his temperature and pulse fell to normal levels, his

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GLYCOGEN DISEASE<sup>1</sup>

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With Plate 21

*Introduction*

THE earliest description of glycogen disease was by Snapper and van Creveld (1928) in a paper entitled 'Chronic Hepatogenic Hypoglycaemia in Childhood' Von Gierke in 1929 published full details of autopsies on two cases and called the condition 'hepato-nephromegalia glycogenica' Since then cases have been described from all parts of the world except the Orient A variety of names has been employed, the ones now in most frequent use being 'von Gierke's disease' and 'glycogen disease' or 'glycogen storage disease' ('Glycogenspeicherkrankheit' (Beumer, 1933)) More recently, Spanish and South American authors have preferred the term 'glycogenic thesaurismosis' (Werner, 1941, Fong, 1942) The essential feature of the condition is the accumulation of excessive quantities of glycogen in the liver, kidneys, or heart muscle Most often, by clinical criteria, the enlarged liver gives the only evidence of the disease, but cases have been described in which only the heart was affected, cardiomegalia glycogenica (Bischoff, 1932, Putschar, 1932, Pompe, 1933) Mason and Andersen (1941) limit the use of the name von Gierke's disease to the hepatomegalic cases with evidence of impairment of the powers of glycogen mobilization At the time of their review they found only 34 examples reported in the literature in which they considered the diagnosis established Since that date cases have been reported by several observers, including Cohen (1942, two cases), Georger (1942), Acuña, Bonduel, and Albores (1942), Ramos and Martínez (1942), Manter and Bowman (1943), Crago (1944), and Martín (1944) The total number reported is thus still under 50 In the present paper a further three cases are described in which a detailed study was made of some aspects of carbohydrate metabolism

*Case Reports*

*Case 1* Male, aged 12 years at the time of these investigations He had been born at full term after a normal labour and had appeared normal at birth There was no history of jaundice or other neonatal ailment The child was breast-fed for 13 months and was then given a mixed diet He cut

<sup>1</sup> Received April 26, 1946

his first tooth at the age of nine months, walked at one year, and could talk a little at the age of one and a half years. Between the ages of six months and one year he had had several attacks of vomiting, but these had ceased spontaneously. It was at the age of 10 months that the child's abdomen was first noticed by the mother to be unusually large. She did not seek medical advice until the boy was three years old, when he started making frequent complaints of epigastric pains occurring usually once a day, particularly after meals. Examined in hospital at that time, he weighed 13.2 kg (normal for age, 14.6 kg) and his height was 81 cm (normal for age, 89 cm). Clinical examination did not show any abnormality of heart, lungs, or nervous system. The abdomen was distended and the greatly enlarged smooth liver extended 9 cm below the costal margin in the right mid-clavicular line. The child was not seen again until he was nine years of age, when his father brought him back to hospital because he was worried about the boy's failure to grow. Epigastric pains had ceased and he had remained well during the six years since his previous examination, and was progressing well at school. His weight was 18 kg (normal for age, 26.8 kg) and his height 102 cm (normal for age, 127 cm), and physical examination revealed essentially the same findings as on the previous occasion, the liver now being palpable 10 cm below the costal margin in the right mid-clavicular line. The Mantoux tuberculin skin test was negative. An X-ray of the carpus showed some delay in the development of the centres of ossification, there were only six carpal centres and the lower ulnar epiphyseal centre had not appeared. The findings thus corresponded to those of a normal child of six years of age. The patient was readmitted to hospital at the age of 12 years when the metabolic studies which are reported below were carried out. He had remained well since the previous visit to hospital and except for his smallness of stature had no complaint. On examination he appeared well nourished and active. His height was 117 cm and his weight 22.8 kg, compared with normal values for his age of 142 cm and 36.2 kg respectively. He corresponded in height and weight to a normal boy of seven years of age. There was no lesion of the skin and the lymphnodes were not enlarged. Examination of the lungs and heart gave normal findings. The apex impulse was in the fourth left intercostal space 5 cm from the mid-line, and radiological examination confirmed the normal size of the heart. The liver was still greatly enlarged, dullness ascending to the sixth rib in the right mid-clavicular line, and the lower border being palpable 10 cm below the costal margin. The spleen and the kidneys could not be felt. Examination of the nervous system did not reveal any abnormality, and an assessment of the intelligence quotient gave a normal result. The Wassermann reaction was negative, the plasma-cholesterol 103 mg per 100 cc and the blood-urea 26 mg per 100 cc. The family history is of interest in this case. A brother of the patient, five years his junior, was also observed in hospital. Similar hepatic enlargement was present and, as a result of biochemical investigations, a presumptive diagnosis of glycogen disease was made. Unfortunately, this child died of measles shortly after he was first seen and it was not possible to complete the observations. An elder sister of the patient was stated to have been 'like the boys' in early childhood. Examined at the age of 15 years, she was normally developed mentally and sexually and was only slightly below the expected height and weight for her age. Her liver, however, was palpable 2 cm below the costal margin and it is possible that she was recovering from the disease. A maternal uncle was also stated to have been like the two boys in childhood, but to have 'grown out of it'.

*Case 2 Female* This child was born at full term and appeared normal at birth. The birth weight was 6 lb. She was bottle-fed on unmodified cow's milk and appeared to thrive during the first year. Walking and talking commenced about the age of one year and she cut her first tooth at 14 months. It was at the age of 18 months that the mother first noticed the child's abdomen to be swollen, and at this time there were frequent and bulky stools, unassociated with pain. The family doctor who was consulted suspected tuberculous peritonitis and prescribed cod-liver oil, which was taken regularly for the succeeding six years. At the age of four years she had had an attack of jaundice which lasted for 10 weeks, but then apparently cleared up completely. She also made good recoveries from measles and whooping-cough in the same year. The child was first brought to hospital at the age of eight years on account of her small size and swollen abdomen. Her height was 106 cm (normal for age, 122 cm) and her weight 17.8 kg (normal for age, 24 kg). On examination she appeared to be in good general health. The skin was normal and there was no lymphnode enlargement. The respiratory and nervous systems appeared to be healthy. The cardiac apex impulse was indefinite in position, but the area of cardiac dullness was within normal limits, and the heart sounds were pure. The liver was greatly enlarged and felt smooth and of firm consistence, it extended 11 cm below the costal margin in the right mid-clavicular line. The right kidney was just palpable, but the left kidney and the spleen could not be felt. The Mantoux tuberculin skin test was strongly positive. An X-ray of the chest showed some vascular congestion of the lungs and slight enlargement of the cardiac shadow. Unfortunately, the child contracted chicken pox while in hospital and had to be discharged before the investigations were completed. Subsequently she attended hospital as an out-patient, but she was not readmitted until she was 13 years of age, when the metabolic studies reported below were made. She had remained well since the previous admission except for occasional vomiting attacks, and her only complaint was of her small stature. Her height was 120 cm (normal for age, 145 cm) and her weight 20.6 kg (normal for age, 36.9 kg). Mental development was slightly retarded (intelligence quotient 79 per cent). Cardiac enlargement could no longer be detected by either clinical or radiological examination, but the liver extended 21 cm below the costal margin in the right mid-clavicular line, and both kidneys were palpable. The spleen was still not palpable. Intravenous pyelography showed considerable enlargement of the parenchyma of both kidneys. In addition to the metabolic studies reported below, the following tests were carried out at this time: Wassermann reaction negative, plasma-cholesterol 239 mg per 100 cc, blood-urea 29 mg per 100 cc, and serum-protein 7.0 gm per 100 cc. Blood cell counts and gastric acidity were normal. When last seen at the age of 13½ years the girl's general health was rather poor, she had grown slightly, but was having attacks of vomiting, usually occurring during the night, once or twice each month. This patient was an only child and there was no history of any similar affection amongst her relatives.

*Case 3 Male*, aged one year and 11 months. The child weighed 8 lb at birth and was breast-fed for eight months. Jaundice was not observed in the neonatal period. He appeared to thrive at first and at the age of eight months he had one tooth and could sit up unaided. Little further progress was made, and at the age of one year and 11 months, when first seen in hospital, he could not stand or walk, and speech was barely commencing. It was with these complaints that his mother brought him to hospital. She

also stated that she had noticed progressive abdominal enlargement since the age of 18 months and that he had had frequent attacks of vomiting since then, and was losing weight. She said that he drank a great deal of water, but did not pass an excessive amount of urine. He had not had any previous illness. On examination he was found to be a fairly well-nourished, pale, flabby child. His weight was 9.5 kg and his height 74 cm compared with normal values for his age of 12 kg and 83 cm respectively. The skin appeared healthy and the lymphnodes were not enlarged. The cardiac apex impulse was palpable in the fourth left intercostal space 5 cm from the

TABLE I  
*Summary of Clinical Features*

	Case 1	Case 2	Case 3
Probable age at onset of symptoms	18 months	18 months	18 months
Primary complaint	Vomiting Abdominal distension	Abdominal distension	Abdominal distension Vomiting
Hepatic enlargement	Extreme	Extreme	Extreme
Renal enlargement	Absent	Present	Present early Absent later
Cardiac enlargement	Absent	Slight early Absent later	Absent
Splenic enlargement	Absent	Absent	Absent
Mantoux test	Negative	Positive	Negative
Family history	Probable cases in siblings	Negative	Negative
*Percentage of expected weight	63	56	92
*Percentage of expected height	82	82	85
Mental development	Normal	Retarded	Normal

\* Calculated from figures obtained at the most recent examination

mid-line, and the heart sounds were pure. Radiological examination confirmed the normal size of the heart. The respiratory and nervous systems did not show any abnormal physical signs. The abdomen was considerably distended. On palpation the liver was found to be greatly enlarged. Its surface was smooth but firm, and it descended to the level of the iliac crest on the right side and to the level of the umbilicus in the mid-line. The spleen was not palpable, but the lower pole of the left kidney could be felt readily. The anterior fontanelle was not quite closed (diameter 0.5 cm), but an X-ray of the wrist showed the two centres of carpal ossification normal at that age. Haematological examination showed a mild hypochromic anaemia (haemoglobin 9.7 gm per 100 cc and red cells 4,760,000 cmm). The Mantoux test and the Wassermann reaction were negative and the plasma-cholesterol was 124 mg per 100 cc. Biopsy of the liver was carried out through a right paramedian abdominal incision. The surface of the greatly enlarged liver was seen to be smooth and of normal colour, and the spleen appeared normal. The specimen for examination was taken from the anterior inferior edge of the organ. Chemical analysis of a piece of the tissue showed the glycogen content to be 7.69 gm per 100 gm of the moist weight. Histological sections stained by haematoxylin and eosin showed the liver cells to be distended and translucent, the nuclei being displaced to the margins of the cells. Preparations fixed in alcohol and stained by Best's carmine showed the majority of the liver cells to be packed with glycogen (Plate 21, Figs 3

and 4), while a frozen section stained for fat showed this substance to be present only in minimal amounts. Unfortunately there was not sufficient tissue available to carry out a chemical estimation of the fat. After the laparotomy the child developed a right-sided basal bronchopneumonia which responded to sulphapyridine administration. He seemed susceptible to respiratory infection and had several mild bronchitic attacks during his stay in hospital. On leaving hospital the child's condition was unchanged. He has since attended as an out-patient and when last seen at the age of eight and a half years his condition showed little change. He had never been really

TABLE II  
*Fasting Blood-Sugar Levels in Glycogen Disease*

Case	Fasting blood-sugar levels, mg per 100 c c			
	49	70	64	—
1	49	70	64	—
2	64	63	61	70
3	52	47	72	54

well and his abdomen had steadily increased in size. Vomiting attacks were occurring about once a month, with occasional diarrhoea. His weight was 24 kg (normal for age, 25.4 kg) and his height 106 cm (normal for age, 124 cm). He appeared very fat, but bright and cheerful and of normal mental development. There was still no evidence of cardiac enlargement and the left kidney, formerly readily palpable, could no longer be felt. The liver occupied the same relative position in the abdomen as before, its lower border passing from behind the right iliac crest to the level of the umbilicus. This patient was the only child of an unmarried woman, the family history was untrustworthy and incomplete, but no history of any similar affection amongst the mother's relatives could be obtained.

Some of the principle clinical features of these three cases are summarized in Table I.

#### *Investigations of Carbohydrate Metabolism*

Morning specimens of urine were tested by the Rothera and ferric chloride tests on numerous occasions. The urine from Cases 1 and 2 gave a brisk positive result with Rothera's test on every occasion, with Case 3 weaker positive results and an occasional negative result were obtained. A positive ferric chloride reaction was never obtained. In each the concentration of ketones in the urine was found to increase after an injection of adrenalin.

Blood-sugar concentrations were estimated by a modification of the method of Hagedorn and Jensen (1923). With this method the fasting blood-sugar levels of normal children were found to lie between 65 and 105 mg per 100 c c, and in 70 per cent of normal children they lay between 75 and 100 mg per 100 c c (Crawford, 1938). In each of the cases of glycogen disease the blood-sugar was estimated under fasting conditions on several occasions. The duration of the period without food varied from eight to 12 hours. The results are shown in Table II. It will be seen that the predominant values are subnormal, but that in each case one value about the lower limit of normal was obtained.



Oral glucose tolerance tests were performed in each case using a test dose of 2 gm of glucose per kilogram of body-weight for the youngest child (Case 3) and 1 gm per kilogram of body-weight in the two older children. The results of the tests are given in Table III and shown graphically in Fig 1. The three curves are remarkably similar to one another. In each curve a peak value is attained in the half-hour or one hour specimen, a fall occurs

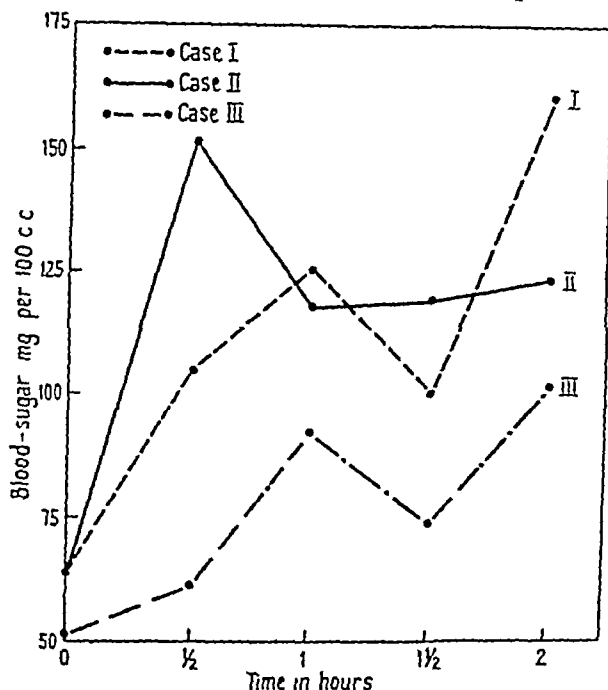


FIG 1 Blood sugar curves after oral glucose in three cases of glycogen disease

in the subsequent specimen, and a secondary rise follows at two hours. The expression biphasic has been used to describe such curves, but 'double-peaked' seems more accurate and less ambiguous. Ketonuria was present both at the beginning and at the end of the test in all, and in none did glycosuria occur.

Intravenous glucose tolerance tests were carried out in each case employing a standard procedure previously described (Crawford, 1938) and used in the investigation of coeliac disease and thyroid disturbances (Crawford, 1939, 1940). The test dose is 0.5 gm of glucose per kilogram of body-weight injected intravenously as a 20 per cent solution in 0.9 gm per 100 cc sodium chloride. Blood-sugar estimations are made two minutes after the injection and at 15-minute intervals for 90 minutes. The results are assessed by observing the time at which the blood-sugar concentration, elevated by the injection, subsides to a level of 100 mg per 100 cc. It has been shown that this time is constant in normal subjects and that in each age-group the normal limits are narrow and sharply defined. In persons over 10 years of age (Cases 1 and 2) the fall to 100 mg per 100 cc should have occurred

within 75 minutes, in a child of two years (Case 3), within 45 minutes. The results of the intravenous glucose tolerance tests in the three cases of glycogen disease are given in Table IV. In Cases 1 and 3 there was definite prolongation of the time required for subsidence of the hyperglycaemia, while in Case 2 the time required was equal to the longest time ever recorded in a normal child of the same age-group. Thus in two of the cases there was

TABLE III

*Oral Glucose Tolerance Tests in Glycogen Disease*

Case	Age in years	Blood sugar, mg per 100 c c						Type of curve
		Fasting	$\frac{1}{2}$ hr	1 hr	$1\frac{1}{2}$ hr	2 hr	Maximum rise	
1	12	64	111	125	101	167	103	High double-peaked
2	13	64	152	117	119	122	88	Prolonged double-peaked
3	2	52	61	92	74	102	50	Prolonged double-peaked

TABLE IV

*Intravenous Glucose Tolerance Tests in Glycogen Disease*

Case	Age in years	Blood-sugar, mg per 100 c c								Type of curve
		Fasting	2 min	15 min	30 min	45 min	60 min	75 min	90 min	
1	12	49	294	270	198	165	125	103	81	Delayed fall
2	13	63	232	193	157	131	111	84	95	Slow normal
3	2	72	239	168	152	134	110	92	—	Delayed fall

impaired tolerance to intravenous glucose while in the third case the tolerance fell just within normal limits.

Blood-sugar curves after the oral administration of laevulose (1 gm per kilogram of body-weight) were carried out in each case. In Case 1 the greatest elevation of the blood-sugar above the fasting value was 29 mg per 100 c c, in Case 2 the rises on two occasions were 17 mg and 5 mg per 100 c c, and in Case 3 the rise was 21 mg per 100 c c. Laevulosuria did not occur in any of the tests. These findings are within the usually accepted limits of normal for the test (Tallerman, 1923).

The effect of a subcutaneous injection of adrenalin hydrochloride was observed in each of the patients and also in a control series of four children convalescent from minor ailments. A test dose of 0.5 c c of a 1:1,000 solution of natural adrenalin hydrochloride from a freshly opened bottle was used in all the children, except Case 2 which received 0.75 c c. In making this test in suspected glycogen disease it is of prime importance to test the adrenalin solution used on a normal subject to make certain of its potency. Several samples have been encountered with no hyperglycaemic action on

normal subjects. The results of the test are given in Table V, and in Fig 2 mean curves are drawn from the patients and the control subjects. In the patients with glycogen disease the increases noted in the blood-sugar level after adrenalin administration were trivial in comparison with those obtained in the control cases. In the former the rise varied from 21 to 37 mg per 100 c.c. whereas in the latter the smallest rise noted was 84 mg per 100 c.c.

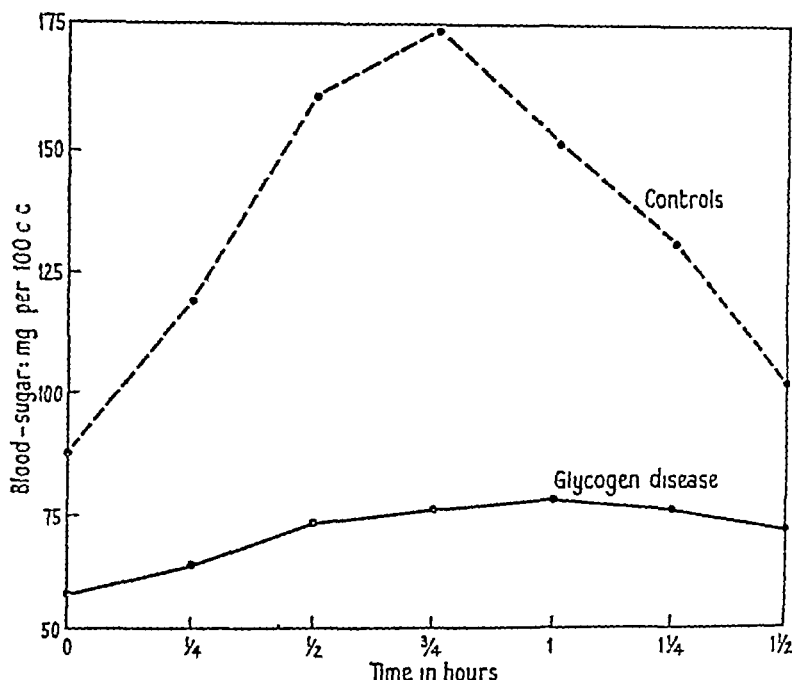


FIG 2 Mean blood-sugar curves after adrenalin injection in three cases of glycogen disease and four control normal subjects

TABLE V

*Blood-Sugar Curves in Glycogen Disease and Control Subjects Following Adrenalin Injections*

Case	Age in years	Blood sugar, mg per 100 c.c.								Maxi- mum rise	Clinical condition
		Fasting	15 min	30 min	45 min	60 min	75 min	90 min	120 min		
1	12	70	83	82	91	88	69	—	—	21	Glycogen disease
2	13	61	63	72	70	75	83	58	—	22	Glycogen disease
3	2	47	52	61	66	77	79	84	65	37	Glycogen disease
A	4	94	131	160	178	164	118	88	—	84	Control
B	8	96	118	143	160	178	181	130	—	85	Control
C	9	80	101	166	190	114	94	90	—	110	Control
D	12	77	128	167	163	—	133	—	106	86	Control

Blood-glycogen levels were determined by the method of van Creveld (1934). Estimations were made in each case of glycogen disease and also in a number

of children with a variety of other diseases The results are shown in Table VI, where they are graded in descending order It will be seen that

TABLE VI

*Glycogen Content of the Blood in Glycogen Disease and Various other Conditions*

Case	Age in years	Blood-glycogen, mg per 100 c c	Clinical condition
3	2	26.6	Glycogen disease
2	13	23.0	Glycogen disease
—	6	13.1	Leukaemia
—	8	7.2	Oesophageal stricture
1	12	6.8	Glycogen disease
—	11	6.6	Diabetes mellitus
—	5½	6.1	Bronchiectasis
—	7	5.0	Tonsillitis
—	7	5.0	Cretin
—	3	5.0	Cerebral diplegia
—	7	5.0	Rheumatism
—	10	4.5	Tonsillitis
—	7½	4.3	Rheumatism
—	10½	3.8	Diabetes mellitus
—	11½	2.0	Cerebral diplegia

TABLE VII

*Plasma and Urinary Diastase in Cases 1 and 2*

Case	Day	Urine			Plasma diastase, units per c c
		Volume, c c	Diastase		
			Units per c c	Total units	
1	1	550	26.5	14,575	—
	2	495	18.5	9,158	7.0
	3	720	19.5	14,040	—
2	1	780	21.0	16,380	—
	2	660	20.0	13,200	8.2
	3	645	19.5	12,577	—

TABLE VIII

*Summary of Results of Investigations of Carbohydrate Metabolism*

Test	Case 1	Case 2	Case 3
Ketonuria (Rothera)	Constant	Constant	Inconstant
Fasting blood sugar	Usually sub-normal	Usually sub-normal	Usually sub-normal
Oral glucose tolerance	Double peaked curve	Double-peaked curve	Double-peaked curve
Intravenous glucose tolerance	Impaired	Slow normal	Impaired
Laevulose tolerance	Normal	Normal	—
Adrenalin hyperglycaemia	Diminished	Diminished	Diminished
Blood glycogen	Normal	High	High
Plasma and urinary diastase	Normal	Normal	—

in two of the cases of glycogen disease the blood-glycogen concentration was far in excess of that found in other conditions In the remaining case (Case 1) the concentration seems to be about the upper limit of normal In only one

other case, a child aged six years with acute myeloblastic leukaemia, was a blood-glycogen above the general level obtained

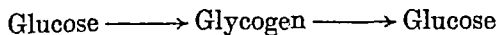
Estimations of the diastatic activity of the blood-plasma and the urine were made by the method of Cohen and Dodds (1924) in two of the cases of glycogen disease. The results are shown in Table VII. They fall well within the normal range of three to 10 units for the plasma and 8,000 to 30,000 units per diem for the urine (Harrison and Lawrence, 1923 a, b)

### *Discussion*

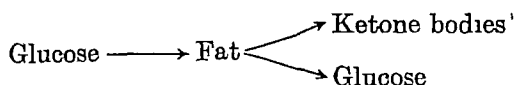
A familial tendency in glycogen disease, as observed in Case 1 of the present series, has been noted previously by Exchaquet (1931), Smith and O'Flynn (1933), Warner (1933), Unshelm (1934), Worster-Drought (1935), Ellis and Payne (1936), and Cohen (1942). The fact that the disease has been found significantly frequently in the children of consanguineous parents (van Creveld, 1939, Unshelm, 1932, Ellis and Payne, 1936) suggests that it may be inherited as a recessive characteristic.

Ketonuria and hypoglycaemia have been found in the great majority of cases of glycogen disease recorded, though in several, as in Case 3, their presence has been inconstant. Lindsay, Ross, and Wigglesworth (1935) reported a case, confirmed by hepatic biopsy, in which ketosis was not present. Opinion regarding the origin of the ketosis of glycogen disease has undergone a change in recent years. Earlier physiologists (Woodyatt, 1910, Shaffer, 1923) regarded ketone bodies as abnormal products of the intermediary metabolism of fat, produced when fat katabolism was proceeding in the absence of a proportionate amount of carbohydrate oxidation. Later work, reviewed recently by Soskin (1941) and Soskin and Levine (1944), has established that ketone bodies are a normal product of fat oxidation, and that considerable quantities are readily utilized by the tissues (Jowett and Quastel, 1935, Wick and Drury, 1941). It has also been shown by extirpation experiments that the liver is the only important site of ketone production (Fischler and Kossow, 1913, Leites and Odnow, 1936, Mirsky, 1936). Clinical ketosis thus occurs in any condition in which the rate of fat katabolism is increased to a level at which the production of ketones exceeds the rate at which they can be oxidized in the tissues. It is essentially independent of the prevailing rate of carbohydrate oxidation. The theoretical possibility that ketosis might result from a failure of peripheral utilization of ketones, even with a normal rate of ketone production, has been investigated by Chaikoff and Soskin (1928), Stadie, Zapp, and Lukens (1940), and Friedemann (1936), but there is no evidence that such a condition occurs. From these considerations it may be deduced that in glycogen disease, with its persistent ketosis, there is a persistently increased rate of fat katabolism. In contrast with this the evidence discussed below indicates that glycogen katabolism proceeds at a subnormal rate or may be almost entirely in abeyance. It

therefore appears that the normal immediate control of the blood-sugar level by the reaction



is taken over in glycogen disease by what is physiologically a secondary and complex reaction



This production of carbohydrate from fat, though for long debated by physiologists, is now a generally accepted occurrence (Soskin, 1941). The ketone bodies produced in this way, while they may lead to acidosis and dehydration when their concentration is high, are not to be regarded as wholly noxious substances. It has been shown that in animals suffering from ketosis utilization of ketones by the tissues may account for as much as 50 to 80 per cent of the oxygen consumption and energy production of the body (Barnes, Drury, Greeley, and Wick, 1940, Wick and Drury, 1941). Glycogen disease thus forms a clear-cut exception to the rule, recently expounded by Mirsky and Nelson (1944), that glycogen stores in the liver are associated with a well-maintained fasting blood-sugar level without ketosis, whereas in the absence of adequate glycogen stores the blood-sugar tends to fall and ketosis develops. In glycogen disease the ketosis and low blood-sugar level are known to be associated with abnormally great stores of glycogen.

The double-peaked blood-sugar curve found after oral administration of glucose in all the present cases has been reported also by van Creveld (1934). All forms of curve, however, have been reported by other workers. Thus, in the case of Lindsay, Ross, and Wigglesworth (1935) the curve was low, while one patient of Schall (1932) exhibited a high prolonged curve. The explanation of these irregular findings is uncertain, they are probably related to irregularities in the rate of absorption and to variations in the glycogen saturation of the liver at the time of the test.

The finding of a greatly increased amount of glycogen in the blood in two of the present cases agrees with results obtained by van Creveld (1934), Schonheimer (1929), Hertz (1933*a*), and Sundal (1936). On the other hand, Schall (1932) and Rauh and Zelson (1934) found diminished amounts, and in Anderson's (1935) case the value was normal. These latter cases, with Case 1 of the present series, are to be regarded as exceptions to the more usual finding. It may be said that the finding of a raised blood-glycogen is important evidence in favour of the diagnosis of glycogen disease, but a normal or low blood-glycogen level does not exclude the possibility of that diagnosis. The only other condition observed to cause considerable elevation of the blood-glycogen is the presence of a greatly increased leucocyte count, as in leukaemia.

Diminution of the hyperglycaemic effect of adrenalin is perhaps the most constant and characteristic feature of glycogen disease, and indeed Mason and Andersen (1941) have accepted as von Gierke's disease only those cases

which showed this feature or gave unequivocal evidence of abnormal persistence of glycogen in the liver at biopsy or autopsy. Many cases reported have shown no rise whatsoever of the blood-sugar in response to adrenalin. There are three possible explanations of such a diminished hyperglycaemic action of adrenalin:

- (1) Hyperinsulinism, causing increased glycogen formation (Wilder, Allan, Power, and Robertson, 1927)
- (2) Absence of a hepatic glycogen store, such as may occur in extreme fatty infiltration of the liver (Bjorum, 1927)
- (3) Defective mobilization of liver glycogen

In glycogen disease the second of these possibilities can be immediately discarded, leaving only the alternatives, abnormally vigorous glycogen formation, as occurs in hyperinsulinism, or failure of glycogenolysis. Results of the intravenous glucose tolerance tests in the present cases show clearly that there is no abnormally active storage of glucose proceeding, the process is in fact somewhat tardy, for the fall of the intravenous curve is delayed in two of the cases. The only other case traced in which a satisfactory intravenous tolerance test has been carried out is that of Mason and Andersen (1941), and here also an impaired tolerance was reported. These findings exclude the possibility of hyperinsulinism or any other cause of rapid glycogen formation being responsible for the accumulation of glycogen in this disease. There remain the two possible causes of failure of glycogenolysis, that the glycogen of the liver and other organs is abnormally resistant to normal glycogenolytic processes, or that there is a failure of action of the hepatic glycogenolytic ferment. While two of the present cases showed normal diastatic activity of the plasma and urine, other investigators (Loeschke, 1932, Hertz, 1933*b*, Rauh and Zelson, 1934, Harnapp, 1936) claim to have found the activity of the blood to be low and that of the urine high. The significance of these findings is doubtful as it is uncertain that the diastatic enzyme appearing in the blood and urine has any connexion with the normal glycogenolytic ferment of the liver.

The question whether the fault lies in the mechanism controlling the formation and breakdown of glycogen has been studied by Mason and Andersen (1941). They showed, in a single case, that glycogen extracted after death from the liver of their patient was normally split by a liver mash from two other subjects, but that a mash prepared from the patient's liver was incapable of breaking down glycogen either from the patient's liver or from any other source. Arguing from their observation, again on a single case, that laevulose and galactose given orally caused no rise of the blood-sugar, whereas glucose caused a high and prolonged rise, Mason and Andersen propounded the hypothesis that the liver is unable to fix glucose, but builds up its enormous glycogen stores from absorbed laevulose and galactose, and that the mechanism for the mobilization of this glycogen is also defective. This hypothesis postulates a double fault in glycogen disease, failure to form glycogen from glucose and inability to convert glycogen formed from

other sources into glucose. The two changes in the reversible reaction  $\text{glucose} \rightleftharpoons \text{glycogen}$  are presumed to be at fault. In the present investigation the blood-sugar curves after oral laevulose administration, though not so flat as the curve obtained by Mason and Andersen, are within normal limits and probably indicate some degree of hepatic glycogen formation from this sugar. In general it may be said that the results of investigations in the present series of three cases are not inconsistent with the hypothesis which Mason and Andersen have introduced.

### *Summary and Conclusions*

Three cases of glycogen disease are described in which a detailed investigation of some aspects of carbohydrate metabolism was carried out. The results of these investigations are summarized in Table VIII. The occurrence of an impaired tolerance to intravenous glucose, an investigation only once previously reported in glycogen disease, is confirmed. From a survey of the available evidence it appears that in this disease the reversible reaction by which glucose is converted into glycogen and glycogen to glucose is at fault. This leads to a greater or less degree of carbohydrate starvation of the tissues with consequent increased metabolism of fat and the production of ketones.

Thanks are due to Professor G. B. Fleming for his valuable criticism and advice, and to the laboratory and clinical staffs at the Hospital for the assistance which they have given.

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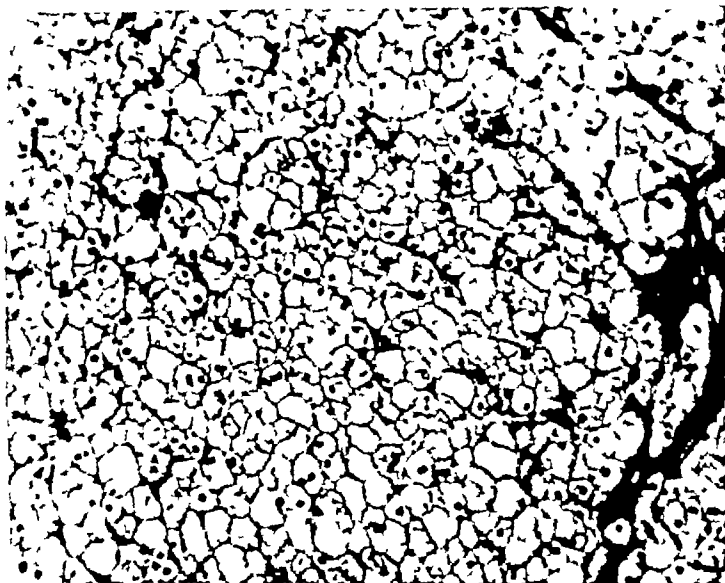


FIG 3

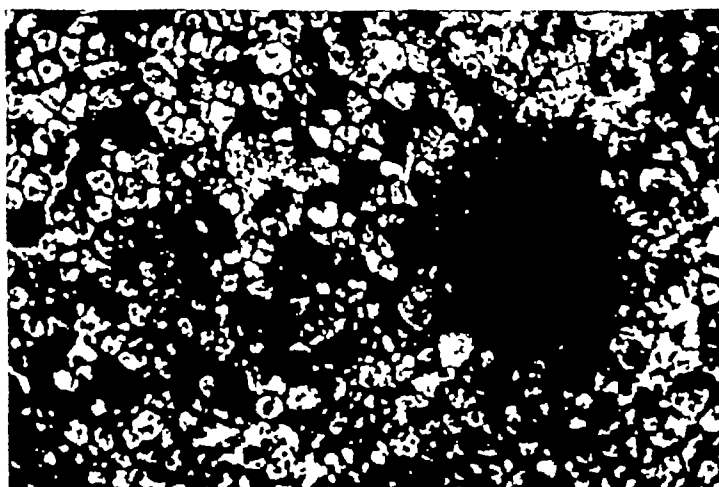


FIG 4

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# THE AETIOLOGY OF CHLOROMA AND THE NATURE OF THE GREEN PIGMENT<sup>1</sup>

## A REPORT OF THREE CASES

By J G HUMBLE

(From the John Burford Carlill Laboratories, Westminster Hospital)

With Plates 22 and 23

THE rarity of chloroma and the fact that it is hardly ever diagnosed during life have rendered obscure many points in the onset and course of the disease. Most of the recorded cases are found in patients suffering from acute myeloid leukaemia, occasional cases occur in chronic myeloid leukaemia (Brannan, 1926), one case is recorded in eosinophilic leukaemia (Seenan and Sajzawa, 1928, cited by Piney, 1939), and there is one case of the condition occurring in monocytic leukaemia (Gump, Hester, and Lohr, 1936). The essential nature of the green tumours is not clearly established, some observers classify them as true neoplasms, others as exaggerations of the infiltrations of leucocytes commonly found in all organs in all types of leukaemia. Their relation to other reticuloses and reticulosarcomata (Robb-Smith, 1938) is given in the Oxford Lymph Node Registry Classification (1946) as myeloblastoma. The nature and significance of the green pigment have been but little studied. The two main opinions of its nature are, firstly, that it is a lipochrome, which apparently originates from the work of Chiarì (1883), and secondly, that it is a blood derivative (Risel, 1902, cited by Ewing, 1940). In the present paper three cases of the disease have been studied. The first in a young man, occurring during the treatment of an apparently typical case of chronic myeloid leukaemia, the second in a young man with primary symptoms of acute testicular disease due to acute myeloid leukaemia, and the third in a woman of 51 years, the subject of monocytic leukaemia. Further, the author has been permitted to study the specimens of Hall (Hall, Hebb, and Bernstein, 1909, Hebb, 1909) and Pulvertaft (1936), which are preserved in the Pathological Museum of the Westminster Hospital School of Medicine. He has also examined, by permission of Dr N H Ashton, a specimen of massive subendocardial chloroma of the heart occurring in a case of eosinophilic leukaemia. On this material the nature of the pigment has been studied chemically and spectroscopically.

### Case Reports

*Case 1 Chloroma complicating chronic myeloid leukaemia during treatment with X-rays* The patient, a young man, was first diagnosed as suffering from

<sup>1</sup> Received June 15, 1946



adherent to the chest-wall and there was an apical empyema containing about 100 c c of pus. Here the upper lobe was collapsed and fibrotic. The mediastinal structures were drawn to the left side. The right lung (610 gm) was congested. The heart (390 gm) was large, due to dilatation of the cavities. There were many subepicardial haemorrhages. The cavities contained bright-green blood-clot. The left ventricular muscle showed 'tabby-cat' striation. The valves and coronary vessels were healthy. The oesophagus, stomach, small intestine, and large intestine were healthy. The liver (2,900 gm) was

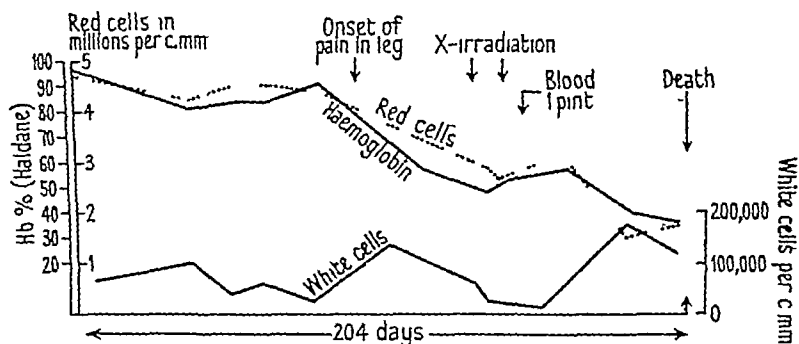


FIG 1 Graph showing the fall in red cells and haemoglobin in Case 1 after the onset of pain in the left thigh

grossly enlarged, yellow in colour, and macroscopically fatty. The gall-bladder and pancreas were healthy. The spleen (2,950 gm) was greatly enlarged. The cut section was homogeneous and dark pink in colour. There were no obvious infarcts. The pituitary, thyroid, and suprarenal glands appeared healthy. The tonsils were of normal size. There was an enlarged haemorrhagic lymph node in the superior mediastinum. In the hilum of the spleen and along the abdominal aorta were several enlarged white lymph nodes. Two green nodes were found at the bifurcation of the aorta. The kidneys were pale but otherwise healthy. There were four small plaques of green tumour lying over the vertex between the dura mater and the skull. The orbits appeared healthy. The brain was congested and the convolutions flattened. There were small deposits of green tumour lying external to the dura mater in the region of the pituitary fossa. The left femur was exposed and removed. It was sheathed in an irregular green tumour mass (Plate 22, Fig 5) which extended from the great trochanter to just above the femoral condyles. On stripping the tumour from the bone, delicate bony spicules extending into it from the bone were found. On section the marrow contained a mass of green material. The knee-joint was not involved. The skull, ribs, sternum, and right patella were similarly packed with green material. A small subperiosteal green nodule was found over the right fibula. All the green material described faded slowly to a dirty yellow colour on exposure to air. The colour could be restored with reducing agents. This green material gave a dull-green fluorescence in ultra-violet light filtered through Wood's glass.

**Histological findings** The material was fixed in 10 per cent formol saline and embedded in paraffin. Frozen sections were cut when indicated. Sections were cut from the tumour mass around the left femur, the kidneys, the spleen, the green lymph node, the liver, the pituitary gland, and the

chronic myeloid leukaemia in June 1939, at the age of 18 years. The white blood count was 600,000 per c mm. He then complained of tiredness and a swelling in the abdomen. The duration of the symptoms was about one month. In 1936 an attack of lobar pneumonia had been followed by a left apical empyema which was surgically drained with resection of part of the sixth, seventh, and eighth ribs, and the resulting sinus never remained healed.

On examination, he was a slim, intelligent young man. The spleen was very large, hard, and extended past the umbilicus. At this time the liver was not enlarged. There were no other abnormal findings. A blood count on December 12, 1939, showed haemoglobin 70 per cent, red cells 3,520,000 per c mm., white cells 112,000 per c mm., polymorphs (neutrophils) 25 per cent, neutrophil myelocytes 78 per cent, and myeloblasts 6 per cent. The blood-film showed a normal number of blood-platelets and a few normoblasts. He was treated with X-rays to the spleen at appropriate intervals and responded well. The red cells rose slowly to 5,530,000 per c mm and the haemoglobin to 102 per cent on June 13, 1941. He remained in good general and haematological condition until October 1942. Between December 1939 and October 1942 32 blood counts all showed chronic myeloid leukaemia. Myeloblasts were found on five occasions only, and their highest level was five per cent of 194,000 white cells on November 14, 1941. In October 1942 he developed a mild anaemia, haemoglobin 78 per cent, red cells 4,100,000 per c mm, and was admitted to hospital. On examination his clinical condition was little changed. He was treated with iron, and left hospital on December 20. A blood count on December 18 showed haemoglobin 86 per cent, red cells 4,200,000 per c mm, and white cells 15,000 per c mm, neutrophil myelocytes 43 per cent, polymorphs 50 per cent, and lymphocytes 7 per cent, and an occasional nucleated red cell was seen in the blood-film. On January 5, 1943, at 3 a.m., he was awakened by a severe pain in the left thigh and both knees. The pain soon left the right knee, leaving a severe, persistent, deep-seated pain in the left thigh. The pain could be alleviated only by morphia. He was readmitted to hospital on January 11. On examination he was pale and ill. The temperature was 100.4°F and pulse 80. There were many petechial haemorrhages on the trunk and legs. There was an ill-defined, tender swelling around the shaft of the left femur, apparently involving the quadriceps femoris muscle. There were many retinal haemorrhages. The liver was palpable. A blood count showed haemoglobin 56 per cent, red cells 3,390,000 per c mm, white cells 149,000 per c mm, blood-platelets 50,000 per c mm, neutrophil myelocytes 68 per cent, and polymorphs 32 per cent. He was treated with vitamin P by mouth, vitamin K by injection, two applications of X-rays to the spleen, and a transfusion of 540 c.c. of blood. An X-ray of the left femur on January 25 showed extensive linear calcification in the soft tissues suggesting an old organizing haemorrhage (Plate 22, Fig 3). He improved slightly and left hospital on February 25, but was readmitted on May 24, and died in coma on May 27, 1943. A further X-ray of the left femur on May 25 had shown considerable roughening of the periosteum (Plate 22, Fig 4). The blood counts from October 1942 to his death are shown graphically in Fig 1. The rapid fall of red cells and haemoglobin after the onset of pain in the thigh is well seen.

The post-mortem examination was performed on May 28, 26 hours after death. The body was that of a moderately well-nourished young man. There was a small sinus immediately posterior to the left axillary fold. The tongue, pharynx, larynx, and trachea were healthy. The bronchi were reddened and contained a little altered blood. The left lung (610 gm) was

physical signs in the chest or central nervous system The abdomen was distended and doughy on palpation Tender and irregular masses could be felt in the left iliac fossa and right midzone The left inguinal lymph nodes were moderately enlarged The liver and spleen were palpable The right testicle was swollen but not painful The prostate was thought to be enlarged The stools were pale The urine contained much bile and a trace of albumin On October 23 a blood count showed haemoglobin 120 per cent, red cells 6,090,000 per c mm, mean corpuscular haemoglobin 27.3  $\gamma\gamma$ , white cells 7,900 per c mm, polymorphs (neutrophil) 70.5 per cent, eosinophils 4.5 per cent, basophils 1 per cent, neutrophil myelocytes 3 per cent, lymphocytes 15 per cent, monocytes 6 per cent, mean corpuscular diameter 7.5  $\mu$  (Eve's halometer), and blood-platelets 176,000 per c mm X-rays of the chest and abdomen on October 24 showed no abnormality Sternal puncture was attempted on October 25, but no specimen of marrow was obtained On October 26 the van den Bergh reaction gave a biphasic direct reaction, indirect reaction 10.3 mg of bilirubin per 100 c c On October 27 no tubercle bacilli were found in a 24-hour specimen of urine On October 29 a blood count showed haemoglobin 93 per cent, red cells 4,520,000 per c mm, volume of packed red cells (Wintrobe) 45 per cent, mean corpuscular haemoglobin 28.3  $\gamma\gamma$ , mean corpuscular volume 95.5 c  $\mu$ , mean corpuscular haemoglobin concentration 28.4 per cent, white cells 10,400 per c mm, myeloblasts 0.5 per cent, neutrophil myelocytes 5 per cent, polymorphs 72.5 per cent, lymphocytes 10.5 per cent, monocytes 4.5 per cent, and Tuck cells 1.5 per cent On October 30 a laparotomy was performed Large fleshy masses apparently of lymph node origin were found in the root of the mesentery and hilum of the liver The omentum contained many deposits A lymph node from the mesentery and a portion of the omental fringe were removed for section A histological diagnosis of reticulosarcoma was made The patient recovered well from this operation He had much nausea, relieved by washing out the stomach From November 5 the urine was free from bile A course of X-irradiation was considered, but on November 12, before any therapy could be instituted, he became much worse On waking he complained of diplopia and showed coarse nystagmus on looking to the right and left There were petechial haemorrhages on the trunk The thyroid gland was found to be moderately enlarged A lymph node was felt in the left supraclavicular fossa The liver and spleen were palpable The temperature was 100.4° F, and pulse 110 The patient died at 12.50 a.m. on November 13 The duration of illness was 36 days

The post-mortem examination was made 12 hours after death The body was that of an emaciated, jaundiced youth The right paramedian incision had healed in the superficial layers, but showed haemorrhage into the deep layers The upper respiratory tract and trachea showed nothing remarkable Both lungs (right 580 gm, left 560 gm) showed much oedema The left lung was adherent to the chest-wall by old adhesions The heart (250 gm) was normal in size and shape The heart muscle, heart valves, and coronary arteries were healthy There were small, flattened, greenish-yellow, subpericardial plaques in the area of the tip of the left ventricle The blood was everywhere fluid and pale except for two small grass-green fibrin clots in the cavities of the ventricles The oesophagus and stomach were healthy The small and large intestines contained much fresh and altered blood The mesentery of the small intestine was greatly infiltrated by a greenish-yellow mass, apparently continuous with a mass of matted lymph nodes around the aorta and vena cava The appendix (five inches in length) was a thick



bone-marrow of the left femur The liver showed periportal infiltrations of immature leucocytes, mainly myelocytes Nucleated red cells were not found The vessels, as in all the preparations, were full of immature and mature granulocytes The liver cells showed some degree of fatty change The kidneys showed some infiltrations of myeloid cells, but these were not prominent The parenchyma was substantially healthy The spleen showed engorgement of the sinuses with red cells and immature granulocytes, the normal splenic architecture was not seen, and the Malpighian centres could not be identified The lymph node showed hypertrophy of the medulla due to the presence of cells similar to those in the tumour, with obliteration of the lymph follicles The sinuses contained immature granulocytes A section stained by Sweet's method showed that the reticulum pattern of the gland was much disorganized, but delicate threads of reticulum were demonstrated throughout the gland Two small venules in the connective tissue around the gland showed well the contents of the blood-vessels throughout the body The bone-marrow of the femur showed fibrous areas containing cells identical with the tumour, alternating with areas of granulopoiesis and active erythropoiesis The pituitary gland was essentially normal, but the meninges around showed invasion by tumour masses resembling the tumour around the femur The femoral tumour presented a different picture from the myeloid infiltrations in the liver and kidney It consisted of large cells, many in mitosis, invading the surrounding muscle At its periphery were many phagocytes containing free iron The tumour cells were large (approximately 15 to 20  $\mu$ ) Some had an oval nucleus, but most a bent or horseshoe nucleus which, in unstained preparations and in May-Grünwald Giemsa-stained sections, had six nuclear spaces The cytoplasm was non granular The nuclear appearance was well seen in sections stained by iron haematoxylin and van Gieson (Plate 23, Fig 6) The tumour cells gave a strongly positive oxidase reaction (benzidine and glacial acetic acid, followed by hydrogen peroxide) The blue colour was not confined to granules in the cells, but coloured the cytoplasm and the nucleus in a uniform manner The tumour cells resembled the cell pictured by Osgood as No 58, 'an atypical granuloblast' (Osgood and Ashworth, 1937), they were not found in the spleen and kidney, and did not resemble the leukaemic cells in the blood-vessels Frozen sections of the tumour did not show granules or aggregations of pigment, or any structures stainable by fat stains

*Case 2 Acute myeloid leukaemia terminating as chloroma* The patient was a young man of 18 years In April 1944 he had an attack of acute left-sided frontal sinusitis lasting one week He had previously been well, except for an attack of mumps in 1943 On October 9, 1944, his right testicle became swollen and painful This was accompanied by frequency of micturition The testicle, epididymis, and vas were swollen, the vesicles and prostate appeared healthy A midstream specimen of urine showed a trace of albumin and an occasional red blood-cell in the centrifuged deposit A tentative diagnosis of tuberculous epididymo-orchitis was made, and he was recommended for admission On October 13 he developed pain in the right side of the chest and in the abdomen The pain was colicky, brought on by food, and associated with nausea and vomiting, but not relieved by it The pain was persistently present, and on October 17 mild jaundice developed He was admitted to hospital on October 21 On examination he was a pallid, thin youth with slight icterus There were petechiae on the soft palate and oozing of blood around the upper left molar There were no abnormal

physical signs in the chest or central nervous system. The abdomen was distended and doughy on palpation. Tender and irregular masses could be felt in the left iliac fossa and right midzone. The left inguinal lymph nodes were moderately enlarged. The liver and spleen were palpable. The right testicle was swollen but not painful. The prostate was thought to be enlarged. The stools were pale. The urine contained much bile and a trace of albumin. On October 23 a blood count showed haemoglobin 120 per cent, red cells 6,090,000 per c mm, mean corpuscular haemoglobin 27.3  $\gamma\gamma$ , white cells 7,900 per c mm, polymorphs (neutrophil) 70.5 per cent, eosinophils 4.5 per cent, basophils 1 per cent, neutrophil myelocytes 3 per cent, lymphocytes 15 per cent, monocytes 6 per cent, mean corpuscular diameter 7.5  $\mu$  (Eve's halometer), and blood-platelets 176,000 per c mm. X-rays of the chest and abdomen on October 24 showed no abnormality. Sternal puncture was attempted on October 25, but no specimen of marrow was obtained. On October 26 the van den Bergh reaction gave a biphasic direct reaction, indirect reaction 10.3 mg of bilirubin per 100 c c. On October 27 no tubercle bacilli were found in a 24-hour specimen of urine. On October 29 a blood count showed haemoglobin 93 per cent, red cells 4,520,000 per c mm, volume of packed red cells (Wintrobe) 45 per cent, mean corpuscular haemoglobin 28.3  $\gamma\gamma$ , mean corpuscular volume 95.5 c  $\mu$ , mean corpuscular haemoglobin concentration 28.4 per cent, white cells 10,400 per c mm, myeloblasts 0.5 per cent, neutrophil myelocytes 5 per cent, polymorphs 72.5 per cent, lymphocytes 10.5 per cent, monocytes 4.5 per cent, and Turek cells 1.5 per cent. On October 30 a laparotomy was performed. Large fleshy masses apparently of lymph node origin were found in the root of the mesentery and hilum of the liver. The omentum contained many deposits. A lymph node from the mesentery and a portion of the omental fringe were removed for section. A histological diagnosis of reticulosarcoma was made. The patient recovered well from this operation. He had much nausea, relieved by washing out the stomach. From November 5 the urine was free from bile. A course of X-irradiation was considered, but on November 12, before any therapy could be instituted, he became much worse. On waking he complained of diplopia and showed coarse nystagmus on looking to the right and left. There were petechial haemorrhages on the trunk. The thyroid gland was found to be moderately enlarged. A lymph node was felt in the left supraclavicular fossa. The liver and spleen were palpable. The temperature was 100.4° F, and pulse 110. The patient died at 12.50 a m. on November 13. The duration of illness was 36 days.

The post-mortem examination was made 12 hours after death. The body was that of an emaciated, jaundiced youth. The right paramedian incision had healed in the superficial layers, but showed haemorrhage into the deep layers. The upper respiratory tract and trachea showed nothing remarkable. Both lungs (right 580 gm, left 560 gm) showed much oedema. The left lung was adherent to the chest-wall by old adhesions. The heart (250 gm) was normal in size and shape. The heart muscle, heart valves, and coronary arteries were healthy. There were small, flattened, greenish-yellow, subpericardial plaques in the area of the tip of the left ventricle. The blood was everywhere fluid and pale except for two small grass-green fibrin clots in the cavities of the ventricles. The oesophagus and stomach were healthy. The small and large intestines contained much fresh and altered blood. The mesentery of the small intestine was greatly infiltrated by a greenish-yellow mass, apparently continuous with a mass of matted lymph nodes around the aorta and vena cava. The appendix (five inches in length) was a thick

yellow rod with a normal lumen. The liver was extremely large (2,600 gm) and on section contained a large amount of bile. The periportal areas were infiltrated with yellow tissue. The main bile ducts were surrounded and compressed by yellow tissue. The pancreas was healthy. The spleen was enlarged (530 gm) and firm. On section, yellow nodules, approximately 3 mm in diameter, were seen embedded in purple splenic tissue. The pituitary and suprarenal glands appeared healthy. The thyroid (50 gm) showed a diffuse colloid enlargement. Enlarged lymph nodes, discrete and white on section, were found in the cervical chains and in both groins. The kidneys (right 200 gm, left 220 gm) were slightly enlarged, dark-green on section, and contained irregular greenish-pink nodules, which on the right side infiltrated the pelvis. The ureters were healthy. The prostate was healthy. The bladder contained a little light-green clear urine. The right testicle was twice the normal size and surrounded by a small hydrocoele. The left appeared normal in size. Neither showed macroscopic changes on section. The brain (1,410 gm) was oedematous and the meninges at the base were tinted green. The orbits contained a grass-green tissue surrounding and infiltrating the globe on each side. The bone-marrow of the ribs, sternum, skull, femur, and vertebral bodies were uniformly yellow-pink on examination. A diagnosis of acute leukaemia with chloromatous change and death from intestinal haemorrhage was made. The green tissue and blood-clot faded slowly on exposure to air. The colour could be restored by reducing agents. The blood was further investigated. A leucocyte count gave 23,000 per c mm, of which 90 per cent were typical myeloblasts, 7 per cent lymphocytes, and 3 per cent polymorphs (neutrophil). On centrifuging, an opaque green plasma separated. The opacity was due to lipid and was removed by shaking with ether. The cleared plasma contained much pseudo-methaemalbumin spectroscopically (confirmed by Schumm's test), and gave 10.3 mg of bilirubin per 100 c c. The green material from the orbits gave a dull-green fluorescence in ultra-violet light filtered through Wood's glass.

*Histological findings.* Sections were cut of the green orbital tumours, the liver, spleen, kidneys, appendix, heart muscle, right testicle, thyroid gland, and the body of the third lumbar vertebra. In addition, the biopsy material, gland and omentum, previously mentioned, was available for study. The orbital tumours consisted of a uniform sheet of cells with round or oval nuclei, with four or six nucleoli, the cytoplasm was relatively scanty and non-granular. Mitoses were frequent and invasion among the fibres of m. levator palpebrae superioris was seen (Plate 23, Fig 7). These cells were remarkably uniform in size (about  $12\mu$ ) and did not resemble the green tumour cells of Case 1. Generally they resembled myeloblasts, and were strongly peroxidase-positive. The liver showed infiltration of the portal tracts with these cells. The parenchyma showed fatty change. The kidney nodules were of the same nature as the orbital tumour. The spleen nodules were of similar nature. The rest of the spleen was much congested. The appendix presented a remarkable picture. The mesentery was grossly infiltrated with the typical cells yet the lumen was not encroached upon. The testicle showed only occasional tubules isolated from their fellows by a mass of tumour cells. The bone-marrow showed a diffuse infiltration with the typical cells, with a few foci of more mature granulocytes and of nucleated red blood-cells. The heart muscle was apparently healthy, but there were subpericardial infiltrations of the typical cells. The lymph node obtained at biopsy showed obliteration of the lymph follicles by a mass of the typical

cells There was extension beyond the capsule The appearances were those of reticulosarcoma and not reticulosis

*Case 3 Chloroma complicating monocytic leukaemia* The patient was an intelligent female aged 51 years Her previous illnesses included appendectomy in 1919 followed by laparotomy for adhesions later in the same year Six months before admission she had had an artificial menopause for 'flooding' In July 1945 she complained of left-sided earache, and X-rays of the teeth were passed as normal In October 1945 an abscess in the root of a left upper incisor tooth discharged through the nose In November 1945 all teeth were extracted The left lower gum became inflamed and was incised This healed well, but an ulcerated nodule remained on the inner aspect of the left lower gum at the level of the absent first premolar This lesion increased a little in size and the left cervical lymph nodes became palpable and tender The patient was admitted to the Westminster Hospital on December 13, 1945 On examination, the lesion on the gum was indurated, resembling an ulcerated carcinoma There were soft mobile lymph nodes in both sides of the neck, the left supraclavicular fossa, and the left axilla The other abnormal finding was that the liver was palpable two fingers' breadth below the costal margin The blood-pressure was 155/85 On December 14 a blood count showed haemoglobin 66 per cent, red cells 3,480,000 per c mm, white cells 6,100 per c mm, neutrophil polymorphs 1 per cent, eosinophils 4 per cent, basophils 1 per cent, lymphocytes 25 per cent, monocytes 61 per cent, monoblasts 7 per cent, and promyelocytes 1 per cent The blood film showed some anisocytosis and polychromasia On December 15 X-rays of the chest and jaw showed no abnormality On December 17 a further white cell count, confirmed by supravital staining (Lightwood, Hawksley, and Bailey, 1934), showed white cells 8,200 per c mm, polymorphs 3 per cent, eosinophils 2 per cent, basophils 2 per cent, lymphocytes 15 per cent, monocytes (including all forms) 50 per cent, monoblasts 28 per cent, and platelets 119,000 per c mm On December 18, 1945 a sternal puncture was performed Total nucleated count 60,000 per c mm, monoblasts 26.8 per cent, promonocytes 17.2 per cent, monocytes 19.6 per cent, and nucleated red cells 11.2 per cent (10.4 per cent normoblasts) The myeloid erythroblast ratio was 1.64:1 On December 20, 1945 the Paul-Bunnell test was negative A diagnosis of monocytic leukaemia was made On January 15, 1946, a blood count showed haemoglobin 52 per cent, red cells 2,760,000 per c mm, white cells 42,000 per c mm, monoblasts 18 per cent, promonocytes 20 per cent, monocytes 46 per cent, eosinophil myelocytes 4 per cent, polymorphs 2 per cent, eosinophils 2 per cent, and lymphocytes 8 per cent The blood-film showed macrocytosis and punctate basophilia On January 29, 1946, the alkali reserve was 59 vols per 100 c c and serum calcium 9.2 mg per 100 c c On February 4, 1946, a blood count showed haemoglobin 36 per cent, red cells 1,750,000 per c mm, white cells 75,000 per c mm, polymorphs 4 per cent, eosinophils 3 per cent, eosinophil myelocytes 3 per cent, lymphocytes 6 per cent, monoblasts 24 per cent, promonocytes 21 per cent, and monocytes 39 per cent The patient's condition slowly deteriorated, but the ulcer on the gum slowly decreased in size The liver increased in size The spleen became palpable and lymph nodes became palpable in the groins and axillae Abdominal masses (para-aortic glands) became palpable The glands became tender and the patient was troubled by vomiting She died on February 24, 1946

The post-mortem examination was performed on February 25, 33 hours

after death The body was that of an emaciated, white-haired woman Enlarged lymph nodes were seen in the inguinal regions, especially in the right side, and on both sides of the neck The submaxillary glands were prominent The abdomen showed two old operation scars, a right paramedian and a right 'grid-iron' scar There were many recent petechial haemorrhages on the abdominal wall The patient was edentulous There was a shallow, almost healed superficial ulcer half an inch in length on the upper aspect of the left ramus of the mandible The tonsils and retropalatal lymphoid tissue were hyperplastic and purple in colour. The tongue was healthy Both submaxillary salivary glands were enlarged On section they were of light-green colour Both cervical lymph node chains were hypertrophied, the nodes were discrete and 'rubbery', the largest was one inch long The chains continued into the mediastinum where many lymph nodes were also haemorrhagic On section they were of varying shades of grass-green The trachea and bronchi were much reddened and contained inhaled material The lungs (right 670 gm, left 700 gm) were bulky and oedematous The terminal bronchioles were 'cuffed' with white material, giving the superficial appearance of miliary tuberculosis The heart (360 gm) was covered on its anterior and posterior aspect with many recent petechiae The pericardium contained 90 c.c. of blood-stained fluid The heart valves and coronary arteries were healthy The heart muscle was pale, but not excessively soft The cavities of the heart contained fibrin clots of a greenish-yellow tint The oesophagus, stomach, and intestines were healthy The liver (2,200 gm) was enlarged, and the periportal tracts showed minute white infiltrations The pancreas was hypertrophied and grass-green on section The spleen (400 gm) was three times the normal size and there was patchy capsular thickening On section a few tiny green nodules were seen on a purple background The pituitary was healthy The thyroid was twice the normal size, homogeneous, and grass-green on section The left suprarenal was healthy, the right contained four small white nodules Enlarged lymph nodes, green on section, were found around the aorta and in both axillae Both kidneys (right 170 gm, left 170 gm) were enlarged, swollen, and on section bright green The cortical markings were much reduced The ureters were healthy The bladder contained 200 c.c. of green urine The uterus and ovaries showed no abnormalities The brain (1,350 gm) was healthy The orbital fat on both sides was curiously hypertrophied and of a yellow colour The marrow of the ribs, sternum, and shaft of the right femur was purple The marrow of the vertebral bodies was tinted green Death was due to monocytic leukaemia complicated by chloroma The thyroid, kidney, and lymph nodes were strongly peroxidase-positive and gave a green fluorescence with filtered ultra-violet light

*Histological findings* The tissues were fixed in 10 per cent formol saline There was, however, evidence of much post-mortem autolysis and a detailed description will not be made It was possible to detect that all the organs examined showed an amazing degree of infiltration with cells of three types This process was best seen in the thyroid gland, where it was difficult to distinguish the scattered thyroid acini among the dense infiltrate The fibrous capsule of the gland was hypertrophied The infiltration consisted mostly of cells resembling mature monocytes, but there were also many eosinophils and eosinophil myelocytes Amongst these there were also many cells with large round nuclei with a small rim of cytoplasm suggesting the monoblasts seen in the peripheral blood during life

*The Pigment of Chloroma*

A study of the available literature showed that little importance has been attached to the green colour of chloroma. The statement, 'it is a lipochrome and contains iron', quoted by most authors, apparently originated with Chiari (1883) according to Kandel (1937). The fading of the pigment on exposure of the tumours to the air has limited investigation, as the pigment was thus believed to be destroyed. Dock and Warthin (1904), Trevithick (1903 *a, b*), and Dustin and Thomas (1938) state that the colour may be restored by the action of solutions of hydrogen peroxide. Only a few cases show this property, in others the colour is discharged even more rapidly than in the presence of atmospheric air. Shennan (1902) restored the green colour partially in the specimens of Dunlop's case (Dunlop, 1902) by means of reducing agents. Pulvertaft (1936) showed that the fading is caused by oxidation, that this may be prevented by keeping the specimens in an atmosphere of hydrogen, or in a solution containing a reducing agent such as sodium hydrosulphite, and that the colour of a previously faded specimen could be restored by this process. He also showed that strong hydrogen peroxide would completely destroy the pigment so that subsequent reduction would not restore the colour. Wilson, working with Pulvertaft, noted that ultra-violet light filtered through Wood's glass caused the fresh tumours, whether oxidized or reduced, to emit a green fluorescence. Dustin and Thomas (1938) and Amano (1939) noted that ultra-violet light caused their specimens to show a reddish fluorescence, and that this was due to the presence of a porphyrin which could be extracted by the method of Dobriner (1937). It was identified by Dustin and Thomas as a protoporphyrin. Both authors believed that the green colour was due to the presence of this porphyrin, although Amano's spectrographic examination of green tumour material does not support this view. Most authors agree that the tumours are peroxidase-positive, that is, they contain a substance which gives a blue colour with benzidine dissolved in glacial acetic acid and hydrogen peroxide, or with similar reagents such as oxidized tincture of guaiacum (Buchanan, 1909). It is generally agreed that the pigment cannot be dissolved out of the tumours by the usual solvents, but Hebb (1909) showed that a green solution could be prepared by warm 0.2 per cent potassium hydroxide solution. Meyer and Berger (1924) stated that glycerin would similarly extract a green pigment. Their solution was stated to show suggestions of absorption bands at  $646.5 \text{ m}\mu$  and about  $490 \text{ m}\mu$ .

The present investigation was carried out on material from the femoral tumour of Case 1. Preliminary experiments were carried out on the fresh material, including an attempt to extract porphyrins by the method of Dobriner (1937), which was completely negative. The tumour mass was then fixed in 10 per cent formol saline, washed with water, cut into small pieces, and dried in a desiccator over calcium chloride. About 5 gm of dried powdered tumour were placed in a 250 c.c. Erlenmeyer flask and 30 c.c. of

20 per cent sodium hydroxide solution (w/v) were added. The flask was placed in a boiling water-bath for 30 min, then cooled, and an equal volume of industrial alcohol added in small volumes with shaking. The solution became turbid. It was then centrifuged at 3,000 revolutions per min for 10 minutes. Five layers were formed, (1) a surface layer, gummy and orange-coloured, (2) a clear layer, (3) a protein disk a few millimetres in depth, (4) a bottom clear zone, and (5) a precipitate of tumour fragments. These layers were separated and examined by the benzidine reaction. The first, second, and fourth layers gave a positive reaction. The upper layer was heated in a water-bath to boil off the alcohol. The tube was cooled and a few milligrams of sodium hydrosulphite added. The gelatinous solution was brown-orange and showed the typical spectrum of a protein-haemochromagen (1 552  $m\mu$ , 2 525  $m\mu$ ). The second layer, similarly treated, showed a similar result with much less pigment concentration. The fourth clear layer, thus treated, gave a green solution which was evaporated to dryness to yield a small quantity of a dark-green pigment having a green fluorescence in filtered ultra-violet light. This was dissolved in 5 c.c. of water with gentle warming and then centrifugalized at 3,000 revolutions for five minutes. This solution became vivid green on reduction with sodium hydrosulphite, and showed green fluorescence in filtered ultra-violet light. Spectroscopically it had three faint absorption bands, closely resembling those of reduced denatured globin cholehaemochromagen, 'green pigment' (Lemberg, Legge, and Lockwood, 1941). This solution was very unstable and rapidly became yellow with oxidation, when the spectrum disappeared. The tumour thus contained both choleglobin and haemoglobin pigments. In this connexion the spectral bands mentioned by Meyer and Berger (1924) suggest those of unreduced green pigment in weak alkali.

Three millimetre slices of the various tumour masses and green tissues were then studied spectroscopically in the reduced glycerine medium of Pulvertaft. The tissues of Case 3 were also studied immediately after removal from the body in the fresh state. Two distinct spectra were found. Cases 1, 2, and 3 and Hebb's Case (Case 3 fresh and after preservation) showed a three-banded spectrum, 1 634.1  $m\mu$ , 2 555.2  $m\mu$ , 3 522.6  $m\mu$ . In each case band 1 was the most intense. Reduced denatured globin cholehaemochromagen in alkali gives 1 616-18  $m\mu$ , 2 562  $m\mu$ , 3 528  $m\mu$ . The second spectrum seen was given by Pulvertaft's Case and Ashton's Case. This was two-banded, 1 594.6  $m\mu$ , 2 508.3  $m\mu$ . All these spectra were measured by means of the Hartridge reversion spectroscope. Amano (1939), by means of a spectrographic technique, described a four-banded spectrum, 1 634.3  $m\mu$ , 2 584.1  $m\mu$ , 3 559.2  $m\mu$ , 4 549.1  $m\mu$ , with absorption in the blue from 478.9  $m\mu$ . The difference between the spectrum of Case 1 and Pulvertaft's Case is illustrated by the simplified absorption spectrum shown in Fig. 2. This was prepared on thin sections using the Lertz 'Leifo' photometer and the range of filters supplied. A striking point is the great rise of absorption in the blue by Pulvertaft's Case as opposed to Case 1. This suggests the

presence of the Soret band of a haemoglobin derivative in Pulvertaft's Case which is absent in Case 1. Cholehaem derivatives do not possess the Soret band. Further, the spleen of Case 1 and the spleen from another case of myeloid leukaemia also showed the spectrum of Case 1. The green urine of Cases 1 and 2, both of which faded on exposure to air, did not show any spectrum even in very thick (25 cm) layers (Buchanan, 1909). These findings

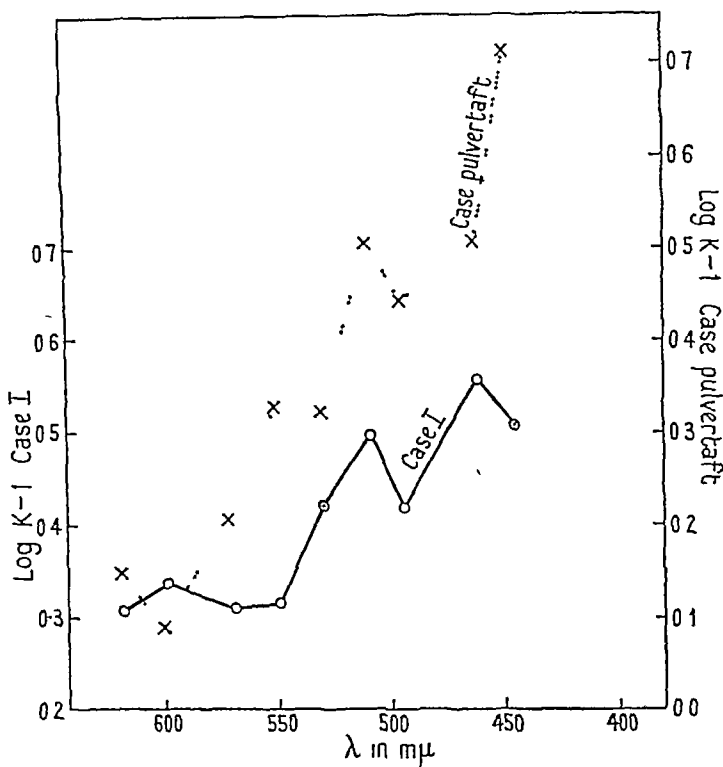


FIG. 2. Simplified absorption spectra of tissues from Case 1 and Pulvertaft's Case

x = Optical density related to a stratum 1 cm. in thickness (extinction coefficient)  
 $\lambda$  = Wave length in mμ

suggest strongly that chloroma pigments are derived from haemoglobin and are choleglobin derivatives. Choleglobin in the living man can be produced only in exceptional circumstances. In theory it could be derived from haemoglobin, cytochrome, or catalase, also possibly peroxidase.

#### Discussion

The three cases described are clearly different both in the nature of their onset and in their clinical course. The morbid anatomy and histology also present many points of difference. Evidence of haemoglobin destruction is seen in the first two cases to a marked degree, both in the femoral lesions of



Case 1 and in the peripheral blood of Case 2, it was not a marked feature of Case 3. In Case 1 a perifemoral haemorrhage was replaced by a green tumour, in Case 2 the post-mortem blood contained much pseudo-methaemalbumin, which is found only when severe intravascular haemolysis occurs. Evidence of red cell destruction was also found by Bamforth and Edwards (1933). It is felt that the essential feature of chloroma is the green pigment and not the cytology of the tumour, which is known to vary from case to case. In this connexion the sternal puncture findings of Osgood (Osgood and Ashworth, 1937) contrast with those of Lightwood (Lightwood, Hawksley, and Bailey, 1934). Osgood depicts a cell in his Atlas (No 58) as a typical cell found in chloroma, adding that similar cells may be seen in acute myeloid leukaemia. Lightwood, Hawksley, and Bailey (1934), using supravital methods as well as Romanowsky stained films, could find no cells peculiar to chloroma. In Case 3 the cytology of the marrow was not obviously different from that of other cases of monocytic leukaemia which the author has studied. Chloromata thus occur in acute myeloid, chronic myeloid, eosinophilic, and monocytic leukaemia. Jones and Jones (1939) in 180 cases were not able to find one case recorded in chronic lymphatic leukaemia. The cell of chronic lymphatic leukaemia is thus different from those of other types of leukaemia in that it cannot, it seems, form this type of green pigment. Chloroma appears to occupy in relation to myeloid, monocytic, and eosinophilic leukaemias the same place that lymphosarcoma does to lymphatic leukaemia. Histologically these green tumours appear to be reticulosarcomata. There does not appear to be any clear evidence in the cases described to incriminate sepsis as an antecedent factor (Goodall and Alexander, 1923).

The problem of chloroma is thus one of cell metabolism and not of cell structure. Little is known of the metabolic processes of leukaemic cells, but Kempner (1939) showed that, provided care was taken not to damage them in any way, myeloblasts showed anaerobic glycolysis, a finding of all normal tissue cells. In view of the occurrence of green tumours at the sites of previous haemorrhage (Bramwell, 1902, and Case 1), one possible explanation is that the chloroma cells invade the haematoma and break down the haemoglobin. A second explanation is that the cells have an abnormal cytochrome system with choleglobin moieties in the prosthetic groups. Amano (1939) stated that his two cases showed spectrographic evidence of cytochrome in the cells and that the green tissue gave a positive Nadi reaction (with p phenylenediamine). He further stated that lymphocytes are Nadi negative and do not give spectrographic evidence of the presence of cytochrome. It is known that the cytochrome system of *B. coli* contains choleglobin (Keilin and Harpley, 1941), and it is possible that the heart muscle preparation described by Keilin and Hartree (1945) also contains a choleglobin moiety in its 'cytochrome A' fraction. Similarly, catalase has been shown to contain a choleglobin fraction (Lemberg and Legge, 1943). *In vitro*, haemoglobin in solution can be rapidly converted into choleglobin by ascorbic acid or by glutathione (Lemberg, Legge, and Lockwood, 1941). There is no doubt that other biological systems

could bring about this change. Catalase appears to prevent this type of degeneration of haemoglobin, for instance, the formation of verdohaemochromagen (Lemberg, 1935) compounds by glucose oxidase and glucose from pure haemoglobin is possible only in the absence of catalase (Keilin and Hartree, 1945). The green pigments observed which can be restored by hydrogen peroxide could be unstable verdohaem derivatives which are yellow when reduced and green on oxidation. Such tissue on exposure to air can be postulated to be oxidized further, strong oxidation yielding verdohaem. In support of this argument is the fact that when ascorbic acid acts on pyridine haemin *in vitro* to give verdohaemochromagen, a porphyrin is set free (Lemberg, Cortis-Jones, and Norrie, 1938). This may account for the findings of Dustin and Thomas (1938) and Amano (1939).

### Summary

- 1 Three cases of chloroma are described
- 2 The similarity of the green pigment to choleglobin derivatives is suggested
- 3 Reasons for attributing the formation of the green pigment to abnormal break-down products of haemoglobin are put forward
- 4 The relation of these green tumours to other leukaemic manifestations is briefly discussed

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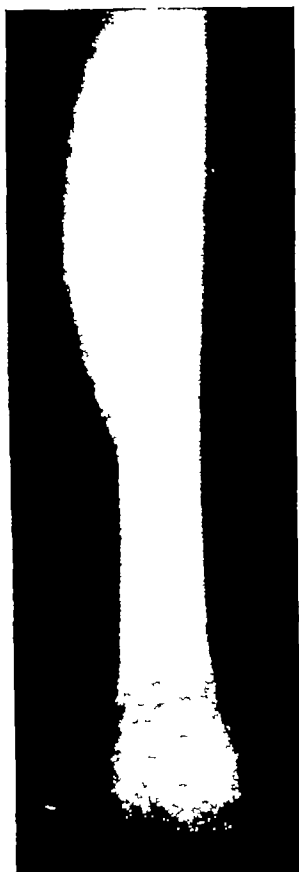


FIG 3



FIG 4





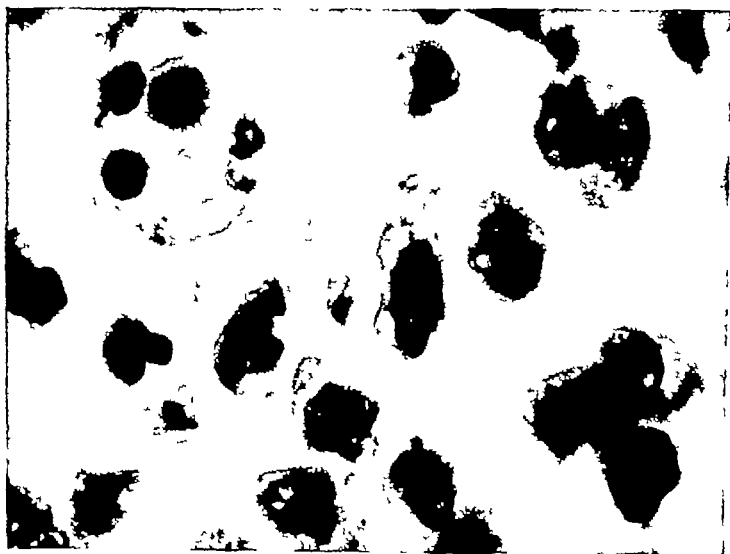


FIG 6



FIG 7



# THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1946

## FORTIETH ANNUAL GENERAL MEETING

THE FORTIETH ANNUAL GENERAL MEETING was held on Friday and Saturday, April 12 and 13, 1946, at Oxford, in the Physical Chemistry Lecture Theatre, South Parks Road. The attendance book was signed by 181 members and 11 visitors. The proceedings began at 9.35 a.m.

*The President*, Dr Gordon M. Holmes, was in the Chair.

*The Minutes* of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read, confirmed, and signed.

*Apologies for absence* were received from Sir Henry Tidy, Dr Izod Bennett, Dr R. R. Trail, Dr Donald Paterson, Dr R. Coope, and Dr G. Riddoch.

Dr Gordon Holmes was elected an *Honorary Member* of the Association with acclamation.

*The Treasurer* presented the annual accounts. He explained that the balance in hand was not really £821, because the Association had not yet received the account from the *Journal*, which would amount to about £450. In 40 years the Association had accumulated capital of about £2,350. The Treasurer recommended a conservative policy until the level of post-war expenditure was known. The accounts were received and adopted.

### *Elections*

*President* Professor A. W. M. Ellis was elected President for 1946-7. On taking the Chair, he proposed a vote of thanks to Dr Gordon Holmes for his services. This was unanimously adopted.

### *Executive Committee*

*President* Professor Arthur W. M. Ellis

*Treasurer* Professor L. J. Witts

*Secretary* Dr C. Newman

### *Members for England*

Sir Adolphe Abrahams  
Dr D. Evan Bedford  
Dr E. Bulmer  
Dr R. C. Clarke  
Professor J. C. Spence  
Sir Charles Symonds

### *Members for Scotland*

Dr J. Craig  
Professor J. N. Cruickshank  
Dr A. Rae Gilchrist

### *Members for Ireland*

Dr R. S. Allison  
Dr T. H. Crozier  
Dr P. T. O'Farrell





Over 95 per cent of these men were traced within six months. Secondly, a 10 per cent random sample of the certified population throughout the coal-field was interviewed in their homes by trained social workers. Thirdly, approximately 200 men were interviewed by a social worker at the time of their medical examination at the Medical Research Council Unit in Cardiff. A detailed analysis of the types of employment done by these men is still in the process of being made.

DR C M FLETCHER, continuing the communication on *Pneumokoniosis, the Clinical and Radiological Findings*, discussed the observations made on 222 ex-coal-miners with certified pneumokoniosis. Radiological progression was assessed by comparing the X-ray taken at the time of certification with the present X-ray. Examples were demonstrated. In 123 cases, with an interval between X-rays of five years and over, it was found that 36 per cent of 49 cases with simple reticulation or nodulation developed advanced fibrosis, while 79 per cent of 84 cases with local shadows had shown advancing fibrosis. While the dust was diffuse, this advancing fibrosis was always focal, and was likely to be due to infection. Younger men were more prone to advance than older men. Subjective clinical deterioration was noted in 65 of 108 cases advancing, and in 34 of 77 cases not advancing. Reduction of vital capacity was observed in most cases, but the degree of reduction did not increase with increasing fibrosis until gross emphysema developed. It was concluded that, to avoid progressive disease, cases should be removed from exposure to dust in the earliest stages of reticulation.

THE PRESIDENT congratulated DR STEWART, the first woman member of the Association, on this happy inauguration of her membership.

DR IVOR DAVIES recalled that although the problem of pneumokoniosis had long been known, little had been done until this investigation started. In the past it had been recognized that colliers were old men, and unemployable, at the age of 50, but few X-ray pictures had been taken, the nature and course of the disease were unknown, and it was regarded as chronic bronchitis and emphysema. He himself had once suggested at a meeting of the Association, in connexion with a communication on chronic vascular changes and respiratory disease, that the responsible factor was changes in temperature, there being often a difference between 80° F in the pit and 40° F in the outside air. Looking back at old X-ray plates, he had found that reticulation was common. He recalled an ex-coller who must have had silicosis, who at the age of 70 years started to cough up coal-dust again and was found to have tuberculosis. He had been struck by the disproportionate cardiac effects in comparison with the radiological lesions and wondered if toxic effects might cause tachycardia. He was not surprised that young men refused to become coal miners, from fear of disease.

DR McMICHAEL recalled that he had visited Hart and Aslitt during their investigation and had found, in the examination of 180 miners, that the measurement of lung volume was a less sensitive index of lung shrinkage than the vital capacity. Coincidentally with the progression of radiological changes there appeared a diminution of vital capacity, but even this became pronounced only in the late stages, with the formation of massive nodules in the lungs, little evidence could be obtained in the early stages. The breathlessness from which these men suffer is not due to deficient oxygenation of the blood, in the case of a porter at his own hospital, who was an old silicotic miner, it was found to be, certainly in part, due to cor pulmonale.

PROFESSOR RYLE congratulated DR FLETCHER's team on achieving so much in so short a time, and commented on the difficulty of an investigation on a population as contrasted with that on an individual, and the necessity of the co-operation of the people studied. He called attention to the unexplained fact that some persons, under precisely the same conditions, do not contract the disease.

PROFESSOR WITTS pointed out that problems such as silicosis are the real clinical problems of our era, a fact which tends to be forgotten by our over-specialized medicine, in which industrial and psychological problems are ignored. He was delighted that the results of turning clinicians and statisticians on to this question should be aired at a meeting of the Association.

DR FLETCHER, replying, paid tribute to DR McMICHAEL, who had introduced him to the medical application of physiology, to PROFESSOR RYLE, his mentor, and to PROFESSOR WITTS, who had grounded him in clinical medicine. He said that he was very conscious of the difficulty of explaining why some men seemed to escape silicosis

*Election of Extra Ordinary Members*

Dr G A Allen  
 Dr A Geoffrey Evans  
 Dr G Hall  
 Professor Adam Patrick  
 Sir Arnold Stott  
 Dr L H F Thatcher  
 Dr G E S Ward  
 Professor O L V S de Wesselow

*Election of New Members*

William Melville Arnott, M D, F R C P (Ed ), Lecturer in Therapeutics, University of Edinburgh  
 Richard Bomford, D M, F R C P, Assistant Physician, London Hospital  
 Denis Hubert Brinton, D M, F R C P, Neurologist, St Mary's Hospital  
 Hector Kenneth Goadby, M D, F R C P, Physician, St Thomas's Hospital  
 Eric Hamilton Hudson, M B, F R C P, Physician, West London Hospital  
 Emyr Wyn Jones, M D, M R C P, Physician to Out-Patients, Liverpool Royal Infirmary  
 James Anthony Waring McCluskie, F R F P S, Temporary Assistant Physician, Glasgow Western Infirmary  
 Alice Mary Stewart, M D, M R C P, Assistant Physician, Elizabeth Garrett Anderson Hospital  
 Charles Herbert Stuart-Harris, M D, F R C P, Professor of Medicine, University of Sheffield  
 Denis John Williams, M D, F R C P, Registrar, National Hospital, Queen Square

*Editors of the Journal* On the recommendation of the Editorial Committee and the Executive Committee in place of Sir Francis Fraser, Professor O L V S de Wesselow, and Dr Donald Hunter, who had resigned, the following were elected as Editors

Dr W R Brain  
 Dr W D W Brooks  
 Dr H L Marriott

It was also agreed that the names of Collaborators should no longer be printed on the cover of the *Journal*

*Re-introduction of Rule 20* It was agreed that Rule 20 should again be put into practice as from the next Annual General Meeting

*Rule 2* It was agreed that, as it had been found that there had not been an exceptional number of proposals due to demobilization this year, the Executive Committee should have power next year, if circumstances indicated the necessity, to exceed the number of eight nominations for Extra Ordinary Membership

*Place of Meeting in 1947* An invitation was received from the local members to meet in Aberdeen. It was agreed that the Association would accept this invitation if circumstances made it possible, but left the decision to the Executive Committee. The Secretary read a letter from the Association of American Physicians, saying that although it had been impossible to arrange a joint meeting of the two Associations in 1946, there was no abatement of enthusiasm for the scheme in America. On a show of hands, 61 of the members present expressed their willingness to endeavour to attend a joint meeting in the United States

## SCIENTIFIC BUSINESS

*Friday Morning, April 12*

DR ALICE STEWART gave the first communication, on *Pneumokoniosis, a field survey The Problems and Methods*. DR STEWART said that in an attempt to study some of the social and economic consequences of the high incidence of pneumokoniosis in South Wales colliers, and to discover whether the disease progresses after the exposure to coal dust has ceased, a clinical and social follow-up of a number of cases certified by the Cardiff Panel of the Silicosis Board was undertaken. Three separate social inquiries were instituted. First, the total certified population from 40 mines in the Rhondda Valley was circularized and the men asked to fill in an Employment Questionnaire



altogether, the men themselves held the pleasing theory that it could be prevented by chewing tobacco and drinking four pints of beer in the evening

DR DONALD HUNTER described *Fluorosis of the Skeleton in workers manufacturing Aluminium in Scotland*. The loss of cryolite to the atmosphere from the aluminium factory at Fort William is about 800 tons per annum. Much of this is in particulate form and settles on the grass around the factory, its distribution varying according to the prevailing wind. As a result sheep and cows in the neighbourhood have developed dental fluorosis with gross irregularity of the teeth. Some of them have died from inanition since they were unable to chew grass. Necropsy on a cow showed 11 fractures of the ribs, and portions of bone contained 0.9 per cent of fluorine, about 20 times the normal figure. Two hundred and sixty-four furnacemen, 80 men from other parts of the factory, 79 local residents, and 124 schoolchildren were examined clinically. Additional investigations included X-rays of the bones, blood counts, and chemical analyses of the urine and blood for fluorine. No X-ray changes were observed in the control group, but there was evidence of skeletal fluorosis in 28 furnacemen. The condition caused no disability even in a man exposed for 42 years. The range of fluorine excretion in the urine in mg per 24 hours was 1.5 to 1.6 in the furnacemen, and 0.5 to 7.9 in other workers in the factory, whereas no local resident or schoolchild was excreting more than 1.5 mg. The blood counts showed no abnormality. The water in Fort William contains less than 0.2 parts per million of fluorine. The investigation is not yet complete. Fluorine has not yet been estimated in the samples of blood taken.

THE SECRETARY asked whether it was true that tea contained appreciable quantities of fluorine.

DR PARKES WEBER asked whether there was any foundation for the suggestion that alopecia may be due to fluorosis of minor degree, and recalled the case of a girl with a suprarenal tumour who became bald after the tumour had been removed, but grew hair again when it recurred.

PROFESSOR WITTS asked whether any changes in the blood had been observed.

DR HUNTER replied that routine blood counts showed no significant changes. There had been a case of aplastic anaemia in a worker in Sheffield who was exposed to fluorine. He told the Secretary that the fluorine content of tea was too low to matter, but that, if he were worried, China tea was a little worse than Indian in this respect.

DR J. J. CONYBEARE gave the results of *A Follow up of Cases of Pleurisy with Effusion in the Royal Air Force*. Eighty-four cases of pleurisy with effusion, presumed tuberculous, which developed between September 1939 and the end of 1941, were retained in the Service. All of these were traced up to the middle of 1945 or later, the period of observation varying from 3½ to 6 years. Of these cases 12 per cent developed pulmonary tuberculosis and 2.5 per cent tuberculous joints in the period of observation. Three were invalided with non-tuberculous disabilities and three were killed in action. Of the 12 cases developing tuberculous disease eight did so within two years.

THE PRESIDENT suggested the importance of adequate rest, in the treatment of pleural effusions, and referred to the significance of the patient's economic status.

DR PARKES WEBER doubted whether an effusion was due to an actual tuberculous pleuritis. In cases of mild tuberculosis he understood that the effusion was thought to be an allergic response to a focus just below the pleura.

SURGEON CAPTAIN BROOKS, R.N.V.R., explained that the Navy, since 1941, had retained such cases for duty on shore. They were re-examined every three months for periods varying from 18 months to three years. One hundred and seventeen men of special value to the Service in whom no parenchymal lesions were found were retained. Their ages were between 17 and 43 years, most were under 25 years. Subsequently, 11 per cent developed clinical tuberculosis, mostly pulmonary, there was only one case of joint disease. A further 21 per cent developed radiological evidence of tuberculosis, but with no symptoms.

PROFESSOR WITTS asked whether it would be right to follow the same plan in the case of nurses.

DR LIVINGSTONE commented on the number of cases which developed clinical symptoms.



*Friday Afternoon*

DR A SLESSOR (introduced by PROFESSOR N MORRIS) speaking on *The insulin sensitivity curve in hypopituitarism* discussed the results of serial estimations of the intravenous insulin tolerance in six cases of hypopituitarism under constant conditions. The blood-sugar response alleged to be characteristic of hypopituitarism, an undue initial fall followed by an incomplete recovery phase, was obtained consistently in one case only. In the others the response was a variable for the individual. Of several tests done on each case, some curves were characteristic of hypopituitarism, while others were normal. Spontaneous variation was also noted in other aspects of metabolism and in the clinical state. The insulin tolerance test may fail to differentiate untreated primary myxoedema from untreated hypopituitarism, but the test carried out during thyroid therapy is apparently conclusive. In primary myxoedema the recovery phase after the initial hypoglycaemia is brisk and sometimes exaggerated, in hypopituitarism it remains slow and is never excessive. It was concluded that owing to the variation which this test may show it should not be regarded as a diagnostic criterion in hypopituitarism nor as a satisfactory means of assessing the results of treatment in this condition.

DR OAKLEY suggested that 10 units of insulin give a very variable response and asked how constant was the response in normal subjects as compared with the average curve shown.

DR HAMILL thought that results on medical students differed from those on other normal subjects.

PROFESSOR HINSWORTH asked whether the work had been done under strictly controlled conditions.

DR GUMPERT asked whether the estimations had been made on capillary blood.

DR SLESSOR replied that there were variations among the responses of normal subjects, but not in the depth of the fall nor in the response to hypoglycaemia. The clinical symptoms varied, a patient who showed mild hypoglycaemic symptoms on one occasion might be severely affected at a subsequent test, but the fall in the blood sugar was constant. The work had been done in strict conditions of complete rest in bed. The estimations had been done on capillary blood.

DR WILFRID OAKLEY described *A case of spontaneous hypoglycaemia due to a diffuse hyperplasia of the islets of Langerhans in a woman of 53 years*. After an unsuccessful operation at which the central portion of the pancreas was removed, the patient was given injections of Young's anterior pituitary extract in increasing doses. In all 2,695 c.c. were given and temporary clinical improvement obtained after each increase in dosage. Hypoglycaemia recurred shortly after injections were stopped. The tail of the pancreas was next removed, without benefit to the patient, and at a later operation as much as possible of the head was resected, this was followed by freedom from symptoms for two years after which attacks recurred. Alloxan was next tried by intravenous injection, 168 gm being given over two short periods. There was intense local reaction with phlebitis and also a severe attack of tetany, but no effect on the hypoglycaemia. Lastly the patient received two courses of deep X-rays to the region of the head of the pancreas. These were followed by definite reduction in the number and severity of attacks.

PROFESSOR HENRY COHEN described *Three cases of unusual Clinical Interest*. The first, a 42 year old man, suffering from subacute bacterial endocarditis, had responded well to penicillin therapy. Several months later he had massive haematuria with slight left lumbar discomfort, and haematuria recurred on several occasions. Examination on readmission to hospital revealed neither a tumour nor bruit in the left kidney region, he was afebrile with no signs of congestive failure and his blood-culture was sterile. An intravenous pyelogram showed a filling defect in the upper part of the pelvis of the left kidney. A diagnosis of aneurysm of the left renal artery was confirmed at operation when nephrectomy was carried out, and the patient remains well. The need for recognizing such sequelae in subacute bacterial endocarditis now that life is prolonged was stressed.

The second patient gave a four years' history of increasingly severe hypoglycaemic attacks, the removal of an islet adenoma of less than 1 cm diameter from the head of the pancreas cured the patient and restored his fasting blood sugar to normal.

The third case illustrated that the fortuitous association of diverse pathological lesions may be of clinical value. A man of 61 years had clinical evidence of the Pel Ebstein syndrome associated with a mass of retroperitoneal lymphnodes. X-ray examination before treatment revealed a calcified abdominal aorta displaced forward by the nodes, after deep radiotherapy the aorta was seen to have returned much closer to its normal position.

LIEUTENANT-COLONEL LARKIN stressed the enormous individual variation to the effects of insulin, 20 units may cause coma, and 200 may not, in different persons. Only a third of patients sweat during insulin shock therapy, and those who 'broke out into a beautiful sweat' do better than those who do not. There seems to be no way of identifying the person who will turn out to be sensitive to insulin. He stressed that pituitary extract and adrenalin during hypoglycaemia were dangerous because they might induce laryngospasm, at any rate, they do not raise the blood-sugar.

DR OAKLEY reminded the meeting that operations and anaesthetics caused hyperglycaemia and asked whether PROFESSOR COHEN's case showed glycosuria.

DR TAYLOR recalled a case of hypoglycaemia in a ballet-dancer whose blood-sugar fell as low as 50 mg per 100 c c, in whom an adenoma of the head of the pancreas was found with the greatest of ease.

PROFESSOR COHEN replied that in his case the blood-sugar rose to 250 mg per 100 c c after operation, and that there was sugar in the urine for a day, but that no acetone appeared in the urine, and that the blood sugar was normal two days after operation. He suggested to LIEUTENANT-COLONEL LARKIN that he preferred the term 'laudable sweat' to 'beautiful sweat'.

The Meeting adjourned to tea at 4 p m after which DR J H SHELDON gave a communication on *Purpura Necrotica—a possible clinical application of the Schwartzman phenomenon*.

Three female children, aged 5 years, 3 years, and 11 months, developed an acute illness whose features were characteristic of allergic purpura. Areas of confluent haemorrhage appeared, having a striking tendency to geometrical shapes, and these subsequently separated as deep sloughs involving the underlying muscles. The condition appeared not to have been previously described, and it was suggested that the shape of the areas might have been due to slight but continued pressure during a critical phase, and imposed by the situation in which the child happened to be during that phase, for example, lying in bed or sitting in a chair. It was thought that the Schwartzman phenomenon gave a closer approximation to the clinical features described.

THE PRESIDENT recalled having seen two or perhaps three cases of indolent ulcer, resembling the photographs shown by DR SHELDON. One had been over the tendo achillis and one on the thigh extending to the buttock, but there had been nothing to suggest that they had been of purpuric origin, they had simply presented themselves as chronic ulcers. He had diagnosed them as due to infection by yeast, but without confirmation.

PROFESSOR MONCRIEFF recalled the case of a purpuric area on the head of a new-born baby followed by a necrotic ulcer. This had probably been caused by pressure during delivery.

DR CLARKE suggested an analogy in deep seated pressure sores, and as bed sores were associated with infections, he wondered whether there appeared to have been infection under the sloughs in DR SHELDON's case.

DR NEALE said he had seen a patient who, after several attacks of abdominal pain, developed necrotic purpura in the skin. As this was presumably a case of Henoch's purpura, he suggested that DR SHELDON's cases also might have had an anaphylactic basis.

DR SCADDING detailed a case of purpura probably associated with minor trauma and pressure in a soldier who had just had a tiger and a scorpion tattooed on his arm. Under treatment for syphilis he developed an (?) arsenical purpura on the sites where his braces pressed, and the tiger and scorpion both became outlined by purpura.



DR SHIELDON thought that the simultaneous case described by DR NEALE suggested that there was a local epidemic in the area. He felt that his cases were quite unlike bed sores. He thought that purpura in the new-born baby might give a clue to the Schwartzman phenomenon as a substance was excreted in the urine which was transmissible to animals.

PROFESSOR R. S. AITKEN described, with two examples, *The clinical picture of the septicæmia and pyæmia due to infection with Bacillus funduliformis*. The characteristic sequence is a sore throat, high remittent fever with prostrating rigors, pleurisy, empyema, and metastatic suppurative arthritis, especially of the sacro iliac joint. The condition is often fatal. The organism can be obtained by anaerobic culture from the blood or the pus, its growth in one instance was inhibited by penicillin. In both cases described, drainage of pus was followed by recovery, the course of the illness in the case treated by penicillin was less severe and more protracted.

DR DOWSETT said he had seen a case of pneumonia in Bristol from which the *Bacillus funduliformis* had been isolated.

THE PRESIDENT thought that this communication put in a plea for anaerobic blood cultures. They were very much neglected and might often be useful.

The Association held its *Annual Dinner* at Rhodes House. SIR WILLIAM GOODENOUGH, PROFESSOR SIR HOWARD FLOREY, and PROFESSOR HANSHELWOOD were present as guests of the Association, and SIR WILLIAM GOODENOUGH proposed the toast of 'The Association', to which the PRESIDENT replied. DR BOYFORD proposed the health of the PRESIDENT.

#### *Saturday Morning, April 13*

DR WILLIAM EVANS, discussing *Innocent Heart murmurs*, emphasized the common incidence of innocent murmurs and of unwarranted cardiac invalidism resulting from it. Such invalidism could be seen in children with restricted activities, recruits exempted from military service, and adults denied entry into occupations of their choice, or rejected from enjoying the security of Life Insurance. He stressed the need and indeed the urgency of assembling for this murmur a clinical and cardiographic pattern which would make its recognition easier and surer. He outlined a clinical classification which had been obtained from a study of 330 healthy subjects at the London Hospital. There were five clinical groups and each was designated according to its main clinical features. The murmur of *reclining posture* was rough and was confined to young subjects, it was uncommon after 30 years and never found after 40 years. The murmur was not loud and for that reason it was often annulled to auscultation by deep inspiration. It was loudest in the reclining posture when a murmur developed in the pulmonary area. The murmur of *upright posture* was common in young subjects and the oldest subject was 43 years. It was rough in character. It was not loud and was best heard in the upright posture. A loud variety of innocent murmur was less common, but since it was fairly loud it was frequently regarded as a sign of mitral disease and for this reason it gained in significance. It occurred in young subjects. Change of posture affected the distribution more than the intensity of the murmur so that in the upright posture it became louder towards the axilla, and towards the base in the reclining posture. The *parasternal* murmur was loud and was best heard in the fourth intercostal space near the left border of the sternum, but it was never accompanied by a thrill as is the case with the murmur of ventricular septum defect. The murmur in *late systole* was loud and rough in character and occurred at all ages. It could be detected easily by clinical auscultation in that the murmur is placed nearer to the second than the first heart sound. The phonocardiogram helped to establish this clinical classification. In the first four varieties the murmur was written in mid systole and in late systole in the last variety. In none was there a diastolic murmur.

THE PRESIDENT was delighted that this communication should have been made before the Association. He opined that the best way to get a good education in these days was to have a diseased heart, avoidance of unnecessary waste of time over games, tuition, and travel gave opportunities for mental and spiritual development.

DR PAUL WOOD thought that attention should be paid to the behaviour of the left auricle in patients with systolic murmurs. In 10 per cent of otherwise normal patients with such murmurs there was expansion of the left auricle and a left axis shift in the electrocardiogram.

PROFESSOR BRUCE PERRY had found that some cases of this kind, if followed up for some time, were found to develop rheumatic heart disease, and it had been reported that during a streptococcal epidemic in a school, children with 'innocent' murmurs showed a higher incidence of rheumatism than the others

DR R E SMITH thought that a good many doctors who examined schoolchildren had had little experience of cardiology, and suggested that when they found murmurs they should refer them to DR EVANS. Once a child was labelled as a cardiac case, it was very difficult to get the label off, and there had even been financial gain from innocent murmurs. He suggested that the blood sedimentation rate should be determined in such cases.

DR COOKSON questioned whether the differentiation could be made with the stethoscope alone

DR EVAN BEDFORD felt that the neurosis engendered by a wrong diagnosis of heart disease was as great a danger as rheumatic heart disease. It was difficult to be certain of the diagnosis, and a doctor should be prepared to run the risk of occasionally mistaking a rheumatic heart. A thrill was not uncommon with a late systolic murmur, and a late systolic murmur was, occasionally, a sign of disease

DR HAWESLEY had found that an enormous number of children were invalided because of growing pains. In a 10 year survey of 1,000 children, 32 per cent had had growing pains at some time, therefore a third of the cases of innocent murmurs would give a history of pains. Some doctors diagnose incipient rheumatism on no other evidence. Neurosis in the Army was often found to be due to the wrong diagnosis of innocent murmurs

DR SCHLESINGER agreed. In the 10 year survey many systolic murmurs disappeared, some patients developed a diastolic murmur and could in time be recognized as suffering from mitral stenosis. He pointed out that a thrill was present only if the murmur was loud. The blood sedimentation rate was a great help. Growing pains were innocent so long as they were confined to the legs

DR EVANS replied that he had examined the left auricles of his patients by barium X ray and found no abnormality. He thought that in the future phonocardiography would be very valuable. He suggested that as some of his patients were over 80 years of age, the follow-up had been adequate, and their murmurs remained unchanged. In Essex any cardiac abnormality in children was reported to him, and a good deal of unnecessary invalidism was, he was sure, avoided. He did not estimate blood sedimentation rates. He thought that too much attention was given to past histories suggestive of rheumatism or chorea. He had seen three cases of organic heart disease which showed incidental late systolic murmurs. He thought that a diastolic murmur did not develop, it was more likely to have been missed at first

SIR ADOLPHE ABRAHAMS, speaking on *Cardiac hypertrophy and physical exercise*, said that the autopsy on a man of 78 years, who died of pulmonary embolus after deep X-radiation for a malignant growth of the thyroid, afforded the opportunity of considering the influence of muscular exercise in the production of cardiac hypertrophy. The deceased had been a remarkable athlete who had indulged in his youth in extreme exertion for many years, and for the rest of his life in fairly strenuous exercise. His blood-pressure in life was not known. Although the analogy of the blacksmith's arm was sometimes advanced, it was generally accepted that provided the musculature was healthy and there was no crippling valvular disease, hypertrophy of the heart did not occur even after the most extreme exertion of which a human being was capable. In this instance a hypertrophied heart weighing 20 oz was found, but the musculature was firm and healthy, the coronary vessels were free from atheroma, and the aorta was exceptionally healthy. All viscera were normal. Two provocative alternatives seemed pertinent. Was it in fact the case that in response to exercise the heart hypertrophied in common with musculature throughout the body? Or did some exceptional individuals possess relatively large hearts and were in consequence constitutionally fitted for protracted exertion?

THE PRESIDENT considered that the total work done by the heart in a patient with a raised blood-pressure over a matter of years was far greater than that necessitated by physical exercise. Hypertrophy certainly did result from a raised blood pressure, but unless the heart failed there was little evidence of the hypertrophy except by radiology

DR SHFDON thought that the simultaneous case described by DR NEALE suggested that there was a local epidemic in the area. He felt that his cases were quite unlike bed sores. He thought that purpura in the new-born baby might give a clue to the Shwartzman phenomenon as a substance was excreted in the urine which was transferable to animals.

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see how there could be any mechanical obstruction in the flow of blood, tying one pulmonary artery in animals produced no rise in pulmonary blood-pressure. Cor pulmonale was often associated with gross oedema of the lungs. Pure mechanical obstruction was not, he felt, more than an insignificant part of the mechanism, the overload on the heart was due more to an increased output. To reduce the output by digoxin or venesection did harm, and he had known one such patient killed by the intravenous injection of digoxin.

PROFESSOR WITTS asked why there was no compensatory polycythaemia.

DR McMICHAEL replied that polycythaemia was extremely rare, certainly, but that he did not know why.

DR CLIFFORD WILSON observed that although the right ventricle was enlarged, the left was not, and if increased output was the essential factor there should, theoretically, be an equal load on both chambers.

PROFESSOR CHRISTIE commented on right ventricular failure without anoxia, and recalled that one of the original cases of cor pulmonale described had not shown cyanosis.

THE PRESIDENT noted that some cases of severe emphysema showed papilloedema, with prominent retinal vessels, and asked if this could be correlated with DR HOWARTH'S observations.

PROFESSOR HIMSWORTH asked what was the blood-volume in the cases discussed.

DR FLETCHER said that mild anaemia was common in association with silicosis of the lungs. He asked if it would be beneficial to give these patients a mild polycythaemia by blood-transfusion.

DR SCHAFER (replying) said that the mechanisms involved were still far from clear. He wondered, particularly, why the venous pressure was raised. He had not seen papilloedema in these cases, but one patient had gross retinal haemorrhages without any great rise in venous pressure. The blood-volume appeared to be normal, and so were haemoglobin figures, but a few were below normal. Transfusion was risky, it might overload the heart and precipitate failure.

DR C C UNGLEY, describing *Peripheral nervous and vascular sequelae to injury by cold*, said that cold sensitivity is common after immersion foot. For several weeks there is complete vasomotor paralysis, and the patient's feet remain hot even when exposed naked in a cool room. Then, on some days, one or both feet are found to be cold. Once cold they tend to remain so despite efforts to induce reflex vasodilatation. This 'algid state' recurs whenever the feet are cooled below a certain level. It persists until environmental or conducted heat raises skin temperature above this critical level, then vasoconstriction passes off and the feet warm rapidly. Once hot, they tend to remain hot, and may be thrust outside the bedclothes, there is often heat sensitivity too. The onset of cold sensitivity seems to coincide with partial re-innervation of skin vessels. Perhaps adrenalin released at intact nerve endings diffuses to vessels, which, being still denervated, are sensitized to this mediator, and the condition seems due particularly to the combined effects of adrenalin and cold.

THE PRESIDENT remarked that he had to be careful to keep his hands warm in Oxford, he even had to warm the newspaper or his hands remained cold till midday.

DR McMICHAEL said that in the case of old polyomyelitis patients a limb hanging down became blue, and in a patient whose median nerve had been cut, and whose fingers in that area of supply had denervated vessels, the hand was warm but cyanotic.

DR BULMER observed that whereas the Navy had made important contributions to this subject, the Army in the recent war had made none. Frostbite had been a scourge in the previous war, but that although the Army in Europe had campaigned through the worst winter in memory, there had been practically no frostbite. Thus, he was sure, was due to better foot discipline and better boots, because other armies in the field had suffered much more severely from frostbite.

DR TAYLOR pointed out that in frostbite actual ice crystals formed in the tissues, whereas in immersion foot this was not so. He had seen a case of what was virtually immersion foot in a Lanarkshire bus driver.

Enlargement of the heart and vessels, in a young man with a short history, was more likely to be caused by malignant than by benign hypertension. The enlargement was degenerative rather than a true muscular hypertrophy. The effects of prolonged benign hypertension supported SIR ADOLPH ABRAHAM'S view.

DR WHITTF described the case of an undergraduate who fell off his bicycle and died, in whom a careful post-mortem examination was done and the results reviewed by other pathologists. The heart (which he showed) weighed 770 gm. The thyroid weighed 30 gm, a finding of doubtful significance. Sections of the heart showed hypertrophy. Nothing abnormal was found in any of the other organs. The young man was a long distance cyclist, but had not played games excessively at school. The case had been published in the *Lancet* in 1934.

PROFESSOR NIXON thought that long distance performers did start with a little bit in hand. They had a low systolic blood pressure. In insurance work it was often found that if a young man had a systolic pressure of under a 100 mm he turned out to be a long-distance athlete. PROFESSOR NIXON thought it was a natural endowment. In the case of a member of the Alpine Club who died at the age of 93 years, having been a good climber over the age of 80 years, whose blood pressure was 120/80, no cardiac hypertrophy was found.

DR PARKINSON asked whether the hearts of athletes were really enlarged. He got that impression from screen examinations. Simple bradycardia would make a heart appear large. He believed that healthy athletes had large hearts.

PROFESSOR MACKRIEFF recalled the thesis written by a student, who rowed, on the size of his own heart during training. After the boat race, and for three years after, his apex beat had enlarged outward  $1\frac{1}{2}$  inches. It took two years to return to normal. It might have been either hypertrophy or dilatation, there was no doubt that it was enlargement.

DR SHARPEY-SCHAFER, considering forms of stress other than physical exercise, pointed out that the heart enlarged as a result of arteriovenous aneurysm. This had been shown to be due to increased output. If one assumed that an athlete rowed for two hours a week, the heart associated with an arteriovenous aneurysm did 10 times as much work. It would need extraordinary violent and prolonged exercise to produce a comparable over-work.

DR JYNER HOSKIN said that since Marathon runners tended to have large hearts, slow pulses, and low blood pressures, it looked as though they had naturally a special type of heart.

SIR ADOLPH ABRAHAM agreed about the findings in Marathon runners, but unfortunately neither radiology nor clinical observation were free from fallacy. He and DR. BRAHWEILL had examined the same athletes in Amsterdam, but did not agree in their findings.

DR S. HOWARTH (introduced by DR. McMICHAEL), describing *The behaviour of the heart in emphysema*, said that the oxygen saturation of the arterial blood falls in the severer grades of emphysema. Clinically, central cyanosis occurs early, followed later by signs of heart failure, raised venous pressure, and oedema. In both phases cardiac output is increased. Terminally, the systolic blood-pressure falls below 100 mm of mercury along with a falling cardiac output. Digitalis and venesection, which lower right auricular pressure, cause a fall in cardiac output, thus emphysema hearts respond to changes in filling pressure like normal hearts, in contrast to low output failures (rheumatic, ischaemic, and hypertensive), which show a rise in output when the venous pressure is lowered. Clinical deterioration is nearly always associated with the fall in cardiac output, venesection and digitalis thus rarely produce clinical benefit and may do harm. The most effective therapy is by oxygen tent, in which patients may be kept for weeks until such precipitating factors as bronchitic exacerbations have subsided. Oxygen therapy may raise the arterial pressure in terminal cases. Thioracil in large and continued doses has given promising results.

DR. McMICHAEL added that when the available oxygen in the venous blood was reduced, the rate of the circulation increased, often because of an increase of the filling pressure. When this was associated with oedema, the picture tended to be regarded as one of congestive heart failure. The capacity of the capillaries in the lung was so great that even when the total number was reduced by emphysema, it was difficult to

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DR WOON said that the injection of adrenalin had no effect on the hot stage of trench foot.

DR CORFMAN added that Lewis's 'triple response' does not occur in these cases

DR BOLAND described similar cases which he had seen in Italy, among South African troops in Rome, where there was a cold wind and the men's feet were cold by day. Occasionally a man's foot would become hyperaemic, and in half an hour the hyperaemia would disappear. At night the feet would become hot and painful, although the temperature of the room was constant. There seemed to be no adequate explanation of this.

DR UNGLEY (replying) said that there was some other factor in the skins of old polyomyelitis patients besides denervation of the vessels. The best demonstration of the difference between frostbite and immersion foot was to be seen in those men who were subjected to cold with their feet in water and their hands in the air, they got immersion feet and frostbitten hands. Even though their hands became gangrenous, there was no anaesthesia in the non gangrenous tissues, and in the feet there was no gangrene, but notable anaesthesia. He agreed that adrenalin was inactive during the first 10 days. Lewis's 'triple response' depended on axon reflexes.

DR W. T. COOKR (introduced by DR PHILIP CLOAKE) spoke on *Liver therapy in idiopathic steatorrhoea*. He said that of a group of 40 cases of idiopathic steatorrhoea, 31 received liver therapy either orally, parenterally, or by both routes. No effect was noted with purified liver extracts (Anahaemin and Examen) and, in general, the haematological response to more crude extracts was variable and unpredictable, bearing no relationship to the presence or absence of megaloblasts in the bone marrow. Reticuloecytosis without rise of red cell count, and *vice versa*, was observed. Only four cases returned to normal blood levels, though macrocytosis and increased fragility were still present. Severe glossitis was noted arising under liver therapy, though on occasions massive injections of crude liver did bring about improvement when all else failed. No quantitative improvement of fat absorption was noted, and radiological abnormalities of the small intestines still persisted after therapy. Even though no objective improvement could be demonstrated, some patients claimed considerable subjective benefit from regular liver therapy.

After the Meeting the Association had luncheon at Magdalen College, when DR GORDON HOLMES publicly thanked the Colleges and others who had made it possible to hold so successful a meeting.

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